

IMAGING AUTISM AND PSYCHOPATHY – TWO VIEWS ON THE SOCIAL BRAIN

TUOMO NOPPARI

UNIVERSITY OF HELSINKI

DISSERTATIONES UNIVERSITATIS HELSINGIENSIS | 497 2026

Faculty of Medicine
University of Helsinki
Dissertationes Universitatis Helsingiensis
497/2026

Imaging autism and psychopathy – Two views on the social brain

Tuomo Noppari

ACADEMIC DISSERTATION
To be presented, with the permission of the faculty of Medicine of the University of Helsinki, for public examination in HUS Psykiatriakeskus Christian Sibelius Auditorium,
on November 27th, 2026, at noon.

Helsinki 2026

At the Department of Psychiatry, Helsinki University Hospital and Turku PET Centre, University of Turku and Turku University Hospital
Doctoral programme in Clinical Research, University of Helsinki

Pre-examiners

Professor Essi Viding, University College London
Professor Vesa Kiviniemi, University of Oulu

Custos

Professor Nina Lindberg, University of Helsinki

Supervisors

Docent Pekka Tani, University of Helsinki
Professor Lauri Nummenmaa, University of Turku
Professor Juha Salmitaival, University of Oulu

Opponent

Professor Essi Viding, University College London

Publisher: University of Helsinki
Series: Dissertationes Universitatis Helsingiensis 497/2026
Cover Image: Markus Lepistö

ISBN 978-952-84-3114-5 (Paperback)
ISBN 978-952-84-3113-8 (PDF)
ISSN 2954-2898 (Print)
ISSN 2954-2952 (PDF)
PunaMusta, Joensuu 2026

To
my daughters
Iiris, Lyydia and Hilda

Abstract

Autism spectrum disorder (ASD) and psychopathy are developmental neuropsychiatric disorders with deficits in social cognition, but markedly different clinical phenotypes. ASD is characterized by persistent difficulties in social communication and interaction, alongside restricted and repetitive patterns of behavior. Psychopathy, in contrast, is characterized by antisocial behavior and callous-unemotional traits with diminished affective responsiveness to others. Despite their distinct phenotypes, ASD and psychopathy share some of their clinical features such as lack of empathy and tendency to aggressive behavior, and there is also evidence on their common genetic basis.

This thesis addresses the question of similarities and differences in ASD and psychopathy from a neuroimaging perspective. We recruited violent offenders with high psychopathic traits, individuals with ASD and neurotypical controls for structural magnetic resonance imaging (MRI, Study I) and functional magnetic resonance imaging (fMRI, Study II). Recordings depicting facial and vocal expressions were used as a task-based fMRI paradigm. Additionally, we performed positron emission tomography (PET) imaging with dopamine D2 receptor (D2R) and mu-opioid receptor (MOR) tracers to study the neurotransmitter mechanism alterations in ASD compared to controls (Study III).

Our main findings were similar structural and functional alterations in the motor cortex in participants with psychopathy and ASD as compared with neurotypical controls. These findings could potentially link to impaired empathy-related processes such as emotional contagion and embodied simulation. Compared to ASD, psychopathy was associated with more pronounced and widespread structural and functional deficits in brain areas related to empathy. Additionally, ASD was associated with lower striatal D2R availability uncoupled with the opioidergic system compared to neurotypical controls. This finding may indicate impaired social reward, motivation and pain mechanisms potentially linked to atypical development of empathy and social interaction in ASD.

In the light of our results, promoting emotional contagion may be an important therapeutic target in enhancing the development of empathy in both psychopathy and ASD, but further research is needed. More research on the positive effects of dopaminergic pathway medication to social cognition is also recommended.

Keywords: Autism Spectrum disorder (ASD), Psychopathy, Magnetic resonance imaging (MRI), Functional magnetic resonance imaging (fMRI), Positron emission tomography (PET), Empathy, Dopamine, Opioids, Social Reward.

Tiivistelmä

Autismin kirjon häiriö (ASD) ja psykopatia ovat kliinisesti toisistaan selkeästi erottuvia kehityksellisiä neuropsykiatrisia häiriöitä, joissa sosiaalisen kognition poikkeavuudet ovat keskeisessä roolissa. ASD:ssä keskeisiä haasteita ovat kommunikoinnin ja sosiaalisen vuorovaikutuksen ongelmat sekä rajoittunut toistava käyttäytyminen. Psykopatialle puolestaan ominaista on antisosiaalinen käyttäytyminen ja tunnekylmät piirteet, sekä vähäinen sosioemotionaalinen reagointi. Vaikka ASD:n ja psykopatian pääasialliset ilmiasut eroavatkin selkeästi toisistaan, niissä on yhdistäviä kliinisiä piirteitä, kuten empatian puute ja taipumus aggressiiviseen käyttäytymiseen. Lisäksi tutkimukset ovat osoittaneet myös yhtymäkohtia näiden häiriöiden geneettisessä taustassa.

Tämä väitöskirja tarkastelee ASD:n ja psykopatian välisiä eroja ja yhtäläisyyksiä aivokuvantamisen näkökulmasta, sillä aikaisempaa vertailevaa tutkimusta on tehty kovin vähän. Tutkimukseen rekrytoitiin psykopaattisia väkivaltarikollisia, ASD yksilöitä sekä neurotyypillisiä verrokkeja aivojen rakenteellista (MRI, Tutkimus I) ja toiminnallista (fMRI, Tutkimus II) magneetti resonanssi kuvantamista varten. FMRI kuvauksen aikana tutkittavat havainnoivat nauhotteita erilaisista kasvojen ja ihmisäänen tunneilmaisuista. Lisäksi tutkimme hermostovälittäjänaineiden toimintaa autismin kirjon häiriössä positroniemissiotomografia kuvauksen avulla käyttäen dopamiini-D2-reseptoriin (D2R) ja mu-opioidireseptoriin (MOR) sitoutuvia merkkiaineita (Tutkimus III).

Pääasiallisina löydöksinämme olivat rakenteelliset ja toiminnalliset poikkeavuudet motorisella aivokuorella, viitaten mahdollisesti heikentyneisiin empatian mekanismeihin; tunteiden tarttumiseen ja keholliseen simulaatioon molemmissa häiriöissä. ASD:hen verrattuna psykopatiassa havaittiin laaja-alaisempia ja korostuneempia rakenteellisia ja toiminnallisia poikkeavuuksia empatiaan liittyvillä aivoalueilla. Lisäksi ASD:ssä D2R sitoutuminen oli vähäisempää ja irti kytkeytynyttä opioidijärjestelmästä verrattuna verrokeihin. Tämä löydös voi viitata heikentyneisiin sosiaalisen palkitsemisen, motivaation ja kivun säätelyn mekanismeihin ja mahdollisesti liittyä epätyypilliseen empatian ja sosiaalisen vuorovaikutuksen kehittymiseen ASD:ssä.

Tulostemme valossa tunteiden tarttuminen saattaa olla tärkeä terapeuttinen kohde empatian kehittymisen vahvistamisessa, sekä psykopatiassa että ASD:ssa, mutta asia kaipaa lisätutkimusta. Suosittelemme myös lisätutkimuksia dopaminergisten lääkitysten positiivisista vaikutuksista sosiaaliseen kognitioon.

Avainsanat: Autismin kirjon häiriö, Psykopatia, Magneetti resonanssikuvaus (MRI), Toiminnallinen magneetti resonanssikuvaus (fMRI), Positroniemissiotomografia (PET), Empatia, Dopamiini, Opioidit, Sosiaalinen palkitseminen.

Acknowledgements

During these six years of my doctoral studies, I have lived through a period of many changes, and there are so many wonderful people to whom I am grateful for making this journey possible.

It all started with my interest in treating aggression in patients with intellectual disability at the Neuropsychiatry Unit of Helsinki University Hospital. The challenging situations encountered in clinical work could occasionally be quite intense, and I soon found myself wondering about the factors underlying such behavior, and in particular about the possible roles of autism and psychopathic traits. I was just about to finish my neurology studies, but I found myself returning time and again to the neuropsychiatry clinic, working under the guidance of my main supervisor, Pekka Tani, and the head physician, Risto Vataja. I had admired their knowledge of combining neurology and psychiatry for many years.

Ever since my medical studies in Turku, I had dreamed of doing research at the Turku PET Centre, but somehow it had never quite happened. Around this time, while working at the neuropsychiatry clinic, I heard an inspiring lecture by Professor Lauri Nummenmaa on bodily maps of emotions and approached him about possible research projects at the Turku PET Centre. Unfortunately, it all again seemed too complicated, as I was still living in Helsinki. However, quite soon afterwards, I heard another fascinating lecture, this time by Professor Juha Salmitaival, on fMRI studies of schizophrenia, ADHD, and autism. This finally convinced me to start my doctoral studies in the Helsinki University Doctoral Programme in Clinical Research.

Around the same time, I had also discussed possible research projects on autism with Pekka and discovered that he and Juha had a joint project of comparing autism and psychopathy using neuroimaging. They had, however, been looking for a suitable doctoral student for some time. Conveniently, I soon learned that Lauri Nummenmaa was also conducting an ongoing neuroimaging project on psychopathy together with Professor Jari Tiihonen and Hannu Lauerma at the Turku PET Centre, and that they were willing to collaborate. Amazingly, everything eventually fell into place, giving me the opportunity to work with all the talented neuroscientists whose work had inspired me and whom I had greatly admired.

Pekka has always been the most temperate and patient supervisor, with a perfect eye and insight for the clinical aspects of our project. He always had the patience to return to the basic research questions, while at the same time to explore new ideas and open new doors. Juha in turn has been one of the most broad-minded and helpful people in answering the many questions that arose during my research. He always had the time to sit down, listen to what I had in mind, and help directing me towards the right path in my work in neuroscience and beyond. Lauri was the driving force of the project, making things happen and keeping the focus on what mattered the most, always pushing forward with great scientific expertise. Despite

his busy schedule, he would still always ask whether I needed any help and find just the right people for me to work with. From the bottom of my heart, I want to thank you all for your inspiring, comprehensive and invaluable guidance into the world of neuroscience.

At the Turku PET Centre, I met my co-researcher Lasse Lukkarinen, who introduced me to the practicalities of neuroimaging and later on helped me in so many ways along the way. Pekka Tani, Juha Salmitaival, Anniina Koski, Vappu Halkola, and Tero Taiminen were instrumental in assisting with the recruitment of participants from the Helsinki and Turku University Hospital and NeuroMental neuropsychiatry clinics, while research psychologist Emma Saure examined all the participants together with me, travelling between Turku and Helsinki.

Finally, the fMRI and PET imaging was made possible by the highly professional crew at the Turku PET Centre. My co-researchers Vesa Putkinen and Kerttu Seppänen together with the radiographers and laboratory technicians Minna Aatsinki, Anne-Mari Jokinen, Tiiina Santakivi, Pirkko Herranen, Tiia Lehtojärvi, Jonna Aarnio, Karri Kivilä, Suvi Hietanen, Sanna Suominen, Heidi Partanen, Tiina Tuominen, Emilia Puhakka, Kia Lehtimäki, worked countless hours with me and Lasse to collect our unique dataset. In addition, neuroradiologist Jussi Hirvonen helped us with the clinical evaluation of the MRI images for any possible anatomical abnormalities. Thank you all for your proficiency, flexibility, and patience during the often busy and unpredictable schedules of our studies.

While working on my first MRI article, Vesa Putkinen played a great role in introducing me to data analysis and the visualization of results. My second fMRI article, in turn, was greatly facilitated by Lihua Sun, as I was merely a lucky apprentice able to follow and learn from his talented approach to scientific work. Thank you both so much for the tremendous effort you put into teaching me the fundamental principles and skills I needed.

Alongside the great Professors Hannu Lauerma and Jari Tiihonen, I also had the opportunity to work with the talented forensic professionals at the Turku Prison Hospital; Niina Venetjoki, Marja Salomaa, and Päivi Rautio. Without your enormous effort, the challenging diagnostic work and recruitment of the offender participants would never have been possible. A special thank you also belongs to Lasse Lukkarinen, who did much of the hard work in organizing the imaging of the offenders, while my main focus was on the autism group of our research project. I want to thank you all for the effective cooperation and for giving me the opportunity to follow and learn from your expertise in forensic psychiatry.

By the time of my third article, I had moved to Turku and had the great pleasure of starting to work with Jouni Tuisku on the PET analyses. Jouni's analytical wizardry was enormously crucial and once again provided me with the perfect opportunity to learn from a true professional. I also finally had the opportunity to work with the rest of Lauri's Human Emotion Systems Laboratory group, as my

research work in Helsinki had mostly been a rather solitary endeavour. Thank you all for your invaluable help, peer support, and friendship.

I want to thank the Department of Psychiatry in Helsinki University Hospital and the Professors in charge, Erkki Isometsä and Tiina Paunio. A humble thank you to my pre-examiners, Professor Vesa Kiviniemi and Essi Viding for the constructive comments. I also want to thank my follow-up group, Professor Hasse Karlsson and docent Tuukka Raij, for the support and help you have given me along the way. A big thank you, of course, belongs to all the participants of the three studies, who made this work possible. I would also like to thank HUS and TYKS government funding, TYKS-Säätiö, Turku University, Lääkäriseura Duodecim, and Professor Lauri Nummenmaa and Nina Lindberg for the financial support of my doctoral studies.

In the end, I want to thank my family and friends. Just a few years before beginning my doctoral studies, I met Martta, the light of my life. She has been supportive and helpful from the very beginning all the way to the end of this project. Without her endless resilience, patience, and understanding, this thesis would never have been possible. During these six years of doctoral studies, alongside completing three articles, I have also been incredibly fortunate to become a father to three daughters: Iiris, Lyydia, and Hilda, my pride and joy. You have all brought so much love and happiness into my life and given me every reason to strive for the best in me. I want to thank my mother, father and sister for their loving care and support trough out my entire life with all the twists and turns. I would also like to thank all my friends for the laughter, friendship, and good times we have shared along the way, always helping to ease my mind when ever needed.

Finally, to everyone who has been part of this journey in one way or another: thank you. This thesis would not have been possible without your support, encouragement, and inspiration.

Tuomo Noppari
23.9.2026 Turku

List of abbreviations

ADHD = Attention deficit and hyperactivity disorder
AQ = Autism spectrum quotient
ASD = Autism spectrum disorder
B_{avail} = Density of receptors available to bind radioligand in vivo, receptor availability
BOLD = Blood oxygenation level dependent signal
BP = Binding potential
BP_{ND} = Binding potential relative to non-displaceable binding
CC = Cingulate cortex
CD/CU = Conduct disorder and callous-unemotional traits
CE = Cerebellum
Cg = Cingulate gyrus
CgG = Cingulate gyrus
dACC = Dorsal anterior cingulate cortex
dlPFC = Dorsolateral prefrontal cortex
DAT = Dopamine transporter
FDOPA = Fluorodopamine [18F]
DMN = Default mode network
DSM = Diagnostic and statistical manual of mental disorders
DTI = Diffusion tensor imaging
D1R = Type I dopamine receptor
D2R = Type II dopamine receptor
FG = Fusiform gyrus
fMRI = Functional magnetic resonance imaging
f_{ND} = Free fraction of the radioligand in the non-displaceable compartment
Fpole = Frontal pole
GP = Globus pallidus
Hipp = Hippocampus
ICD = International statistical classification of diseases and related health problems
IFG = Inferior frontal gyrus
INS = Insula
IOC = Inferior occipital cortex
IOG = Inferior occipital gyrus
IPL = Inferior parietal lobule
IQ = Intelligence quotient
ITG = Inferior temporal gyrus
K_D = Dissociation constant
$1/K_D$ = affinity of the radioligand
latPFC = Lateral prefrontal cortex
LMM = Linear mixed-effects models
LSRP = Levenson self-report psychopathy scale

M1 = Primary motor cortex
M2 = Secondary motor cortex
MCC = Middle cingulate cortex
MOR = Mu-opioid receptor
mPFC = Medial prefrontal cortex
MRI = Magnetic resonance imaging
MTG = Middle temporal gyrus
Nacc = Nucleus accumbens
OcG = Occipital cortex
OFC = Orbitofrontal cortex
PCL-R = Psychopathy checklist-revised
PCUN = Precuneus
PET = Positron emission tomography
PFC = Prefrontal cortex
PostCG = Postcentral gyrus
PreCG = Precentral gyrus
PreCu = Precuneus
PreSMA = Pre-supplementary motor area
ROL = Rolandic operculum
ROI = Region of interest
rs-fMRI = Resting-state fMRI
S1 = Primary somatosensory cortex
S2 = Secondary somatosensory cortex
SMA = Supplementary motor area
SMN = Sensorimotor network
SPL = Superior parietal lobule
SRTM = Simplified reference tissue model
STS = Superior temporal sulcus
TFUS = Temporal fusiform gyrus
ToM = Theory of mind
VBM = Voxel-based morphometry
vmPFC = Ventromedial prefrontal cortex
V_{ND} = Volume of non-displaceable ligand in tissue
VT = Total distribution volume of ligand in tissue

Index

Abstract v
Tiivistelmä vi
Acknowledgements vii
List of abbreviations x
A. Introduction 1
B. Review of the literature 2
1. Social Cognition 2
2. Imaging of social cognition 3
2.1. Human brain imaging 3
2.2. Structural imaging of social cognition 6
2.3. Functional imaging of social cognition 7
2.4. Molecular imaging of social cognition 11
2.4.1. Dopamine system 11
2.4.2. Opioid system 12
2.4.3. Oxytocin system 13
2.4.4. Serotonin system 13
2.4.5. Interregulatory neurotransmitter connections 13
2.4.6. Neurochemistry of aggression 14
3. Autism spectrum disorder 14
3.1. Structural imaging of ASD 17
3.2. Functional imaging of ASD 19
3.3. Molecular imaging of ASD 21
3.3.1. Dopamine system 21
3.3.2. Opioid system 21
3.3.3. Serotonin system 22
3.3.4. Other transmitter systems 22
4. Psychopathy 22
4.1. Structural imaging of psychopathy 26
4.2. Functional imaging of psychopathy 26
4.2.1. Social tasks 27
4.2.2. Non-social tasks 27
4.3. Molecular imaging of psychopathy 28
5. Similarities and differences between ASD and psychopathy 29
5.1. Structural imaging of ASD and psychopathy 33
5.2. Functional imaging of ASD and psychopathy 34

5.3. Molecular imaging of ASD and psychopathy 34
C. Objectives 35
D. Materials and methods 35
1. Subjects 35
1.1. ASD group 36
1.2. Violent offender group 36
1.3. Control group 37
2. Overall study design 39
3. Methods 40
3.1. Study I 40
3.1.1. Statistical analysis 40
3.2. Study II 40
3.2.1. Statistical analysis 42
3.3. Study III 42
3.3.1. Statistical analysis 44
3.3.2. Meta-analysis 44
E. Summaries of the original studies 45
1. Study I: Brain structural alterations in autism and criminal psychopathy 45
1.1. Results 46
1.2. Conclusions 47
2. Study II: Aberrant motor contagion of emotions in psychopathy and high-functioning autism 47
2.1. Results 48
2.2. Conclusions 50
3. Study III: Aberrant type 2 dopamine and mu-opioid receptor availability in autism spectrum disorder – Abnormal opioid-dopamine interaction in autism 50
3.1. Results 50
3.2. Conclusions 52
F. Discussion 52
1. Impaired empathy mechanisms as a unifying factor for psychopathy and ASD 52
2. Dysfunctional social reward, motivation and pain in the atypical development of empathy in ASD 54
3. Clinical implications 56
4. Strenghts and limitations 59
G. Conclusions and future perspectives 60

References **62**
Original publications **104**

List of original publications

This thesis is based on the following publications:

I. Noppari T, Sun L, Lukkarinen L, Putkinen V, Tani P, Lindberg N, Saure E, Lauerma H, Tiihonen J, Venetjoki N, Salomaa M, Rautio P, Hirvonen J, Salmi J, Nummenmaa L. (2022). Brain structural alterations in autism and criminal psychopathy. Neuroimage Clinical. 2022;35:103116. doi: 10.1016/j.nicl.2022.103116.

II. Sun L, Lukkarinen L, Noppari T, Nazari-Farsani S, Putkinen V, Seppälä K, Hudson M, Tani P, Lindberg N, Karlsson HK, Hirvonen J, Salomaa M, Venetjoki N, Lauerma H, Tiihonen J, Nummenmaa L. (2022). Aberrant motor contagion of emotions in psychopathy and high-functioning autism Cerebral Cortex. 2022 Dec 20;33(2):374-384. doi:10.1093/cercor/bhac072.

III. Noppari T, Tuisku J, Lukkarinen L, Tani P, Lindberg N, Saure E, Lauerma H, Tiihonen J, Hirvonen J, Helin S, Rajander J, Salmi J, Nummenmaa L. (2025). Aberrant type 2 dopamine and mu-opioid receptor availability in autism spectrum disorder. European Journal of Nuclear Medicine and Molecular Imaging 2026 Feb;53(3):2069-2082. doi: 10.1007/s00259-025-07620-5.

A. Introduction

Humans are inherently social beings, and the ability to engage in social interaction is fundamental to functioning in contemporary society. Social cognition encompasses the cognitive and affective processes that enable individuals to perceive, interpret, and respond to the social world (Henry et al., 2016). These processes are supported by a distributed set of brain regions forming a large-scale social brain network (Fernández et al., 2018). Neurotransmitter systems, including dopamine and endogenous opioids, play a modulatory role in social cognition and social motivation (Kyte et al., 2020; Padilla-Coreano and Martínez-Rivera, 2025).

ASD and psychopathy are neurodevelopmental conditions characterized by atypical social cognition, but with markedly different clinical phenotypes (Murphy et al., 2024). ASD is characterized by persistent difficulties in social communication and interaction, alongside restricted and repetitive patterns of behavior (Hirota and King, 2023). Psychopathy, in contrast, is characterized by antisocial behavior and callous-unemotional traits with diminished affective responsiveness to others (De Brito et al., 2021a). Despite their distinct phenotypes, ASD and psychopathy share certain overlapping features, including impairments in social functioning, partially shared comorbidities, and evidence of common genetic influences (De Brito et al., 2021a; Hirota and King, 2023; Murphy et al., 2024; Tiihonen et al., 2020).

Neuroanatomical studies have identified prominent alterations in fronto-temporal regions in both ASD and psychopathy (Boedhoe et al., 2020; Johanson et al., 2020; Van Rooij et al., 2018), and functional neuroimaging studies have demonstrated atypical activation patterns within social brain networks during social cognitive tasks (Berluti et al., 2023; Di Martino et al., 2009; Dickstein et al., 2013; Dugré et al., 2020; Goodwill et al., 2023; Lenzen et al., 2021; Patriquin et al., 2016; Penagos-Corzo et al., 2022). However, the neurochemical underpinnings of these conditions remain poorly understood (Kolla and Houle, 2019; Lam et al., 2006; Marotta et al., 2020). Evidence from both animal and human studies suggests that dopaminergic and endogenous opioid systems may play a role in the etiology of ASD (Dichter et al., 2012; Fuccillo, 2016; Oddi et al., 2013; Pellissier et al., 2018) and psychopathy (Bandelow and Wedekind, 2015; Glenn and Yang, 2012; Tiihonen et al., 2020; Wu and Barnes, 2013; Yildirim and Derksen, 2015a), but also in aggressive behaviors that may occur in individual with either condition (Feltes and De Boer, 2021; Umukoro et al., 2013).

To date, only a limited number of neuroimaging studies have directly compared ASD and psychopathy. Comparative research is therefore needed to clarify both shared and disorder-specific neurobiological mechanisms underlying aberrant social cognition. By examining ASD and psychopathy as two contrasting views on social cognition, the present work aims to elucidate their disorder-specific and shared neurobiological foundations using multimodal neuroimaging approach, including structural MRI, fMRI, and PET.

B. Review of the literature

1. Social Cognition

Social cognition is one of the six core components of neurocognitive functioning (American Psychiatric Association, 2013). It is an umbrella term referring to our ability to understand other´s emotions, thoughts and intentions and to empathize with them and to behave accordingly (Magno et al., 2022). The definitions, terminology and measurement for social cognition have been inconsistent in the scientific literature (Wallis et al., 2022), but it can be categorized into four different clinical domains; social perception, empathy, theory of mind (ToM), and social behavior (Henry et al., 2016).

Social perception includes recognizing and interpreting emotional and social cues such as facial expressions, body language, voice and eye gaze (Henry et al., 2016).

Empathy refers to the capacity to reflect mental states of others and it can be divided into three different components: motor, emotional (affective) and cognitive empathy (Blair, 2005a; Cuff et al., 2016; Gallese, 2003). Motor empathy refers to unconscious and automatic mimicry and synchronization of facial expressions, vocalizations, postures, and movements of another person (Blair, 2005a; Hatfield et al., 1993). Emotional empathy in turn refers to sharing of feelings, emotional resonance and experience of emotions consistent with and in response to those of others (Bons et al., 2013; Cuff et al., 2016; Henry et al., 2016). Emotional contagion is a precursory process for empathy and in close relation to the emotional and motor components (Bulgarelli and Jones, 2023; Hatfield et al., 1993; Niedenthal, 2007). Finally, cognitive empathy refers to the ability to rationally understand and recognize the emotional state and take the perspective of other persons (Blair, 2013; Bons et al., 2013; Cuff et al., 2016; Henry et al., 2016).

ToM implies to the ability to mentalize or to understand mental states, intentions, goals and beliefs of others, irrespective of their emotional states (Henry et al., 2016; Korkmaz, 2011). ToM relates, for instance to joint attention and understanding deception, metaphor and sarcasm (Korkmaz, 2011). ToM can be further divided in emotional (affective) and cognitive parts (Henry et al., 2016). The emotional part requires understanding of emotional states and feelings of others partly overlapping with cognitive empathy, whereas the cognitive part requires understanding of others cognitive states, beliefs, thoughts and intentions (Henry et al., 2016).

Social behavior emerges as a response to perceived social cues and result of empathic and ToM processes, which is further modulated by reward processing, emotion regulation, and executive functions. The definition and structure of executive functions is largely debated, but its core can be summarized into inhibition (impulse control), interference control (selective attention), working

memory and cognitive flexibility (Diamond, 2013; Nigg, 2017). Cognitive flexibility refers to our ability to switch between different tasks, change our perspective and adjust our behavior to the current environment (Diamond, 2013).

Aggression is a practical example of maladaptive impulse control and lack of cognitive flexibility that is relevant in the context of this thesis. Aggressive behavior has promoted evolutionary survival of the human race, but in our contemporary society it is legally controlled and regarded as inappropriate (Meloy, 2025). It can be divided to two different modes, reactive (impulsive, affective) and proactive (predatory, instrumental), where proactive aggression has a stronger genetic origin (Meyer-Lindenberg et al., 2006). Reactive aggression is a behavioral response to a provocative social cues and negatively associated with empathy and ToM processing in children (Pouw et al., 2013; Romero-Martínez et al., 2022; Wang et al., 2023). It is characterized by negative affect and is a result of dysfunctional emotion and poor impulse control (Bertsch et al., 2020; Hecht and Latzman, 2018; Romero-Martínez et al., 2022). In turn proactive aggression is callous (low arousal) and instrumental goal-directed behavior used to gain benefit and reward (Hecht and Latzman, 2018; Romero-Martínez et al., 2022). It is negatively associated with ToM and affective empathy, but the associations with cognitive empathy are unclear in children (Pouw et al., 2013; Wang et al., 2023). Dysfunctional self-regulation and executive functions are not characteristic for proactive aggression and moreover it has been associated with higher levels of working memory (Hecht and Latzman, 2018).

2. Imaging of social cognition

2.1. Human brain imaging

Magnetic resonance imaging (MRI) can be used to create tomographic images of the brain structure. Charged nuclear particles, such as protons have a fundamental property of spinning about itself and forming an electric current with magnetic momentum. The net magnetization of a volume can be changed by organizing spins of proton in parallel high energy or antiparallel low-energy states with a strong magnetic field and radiofrequency wave pulses. These changes in the electromagnetic energy produce the detected MRI signal (**Figure 1**). Different tissues, such as grey and white matter, have different kind of electromagnetic properties that can be separated from each other by using radiofrequency pulses and gradient magnetic fields providing tissue-specific contrasts. The most commonly used structural contrast is T-weighting (T_1, T_2), which is based on the different relaxation time of the spin in certain tissues (Huettel et al., 2004). Voxel-based morphometry (VBM) is an automated technique for identifying regional alterations in whole brain T1-weighted images, allowing volumetric regional comparison between groups (Whitwell, 2009). Since there is a great variance in the

human brain anatomy, the T1-weighted images need to be normalized to the same stereotactic space for comparison between subjects. Images are also smoothed to improve signal-to-noise ratio and the grey and white matter are analyzed separately in VBM (Ashburner and Friston, 2000).

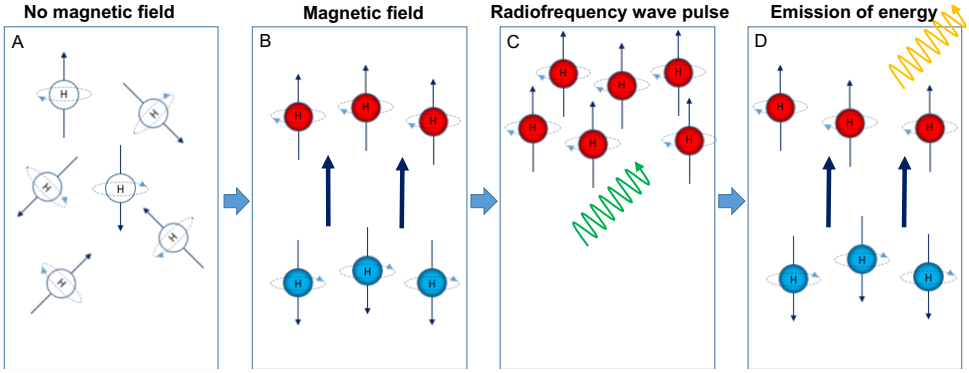


Figure 1. A. Protons randomly oriented in the tissue in the absence of magnetic field. B. Protons aligned to the magnetic field (black arrow) in high- (red) and low-energy (blue) states in magnetic field. C. Radiofrequency wave pulses (green arrow) transfer protons to high-energy states. D. Protons returning to low-energy states emit energy (yellow arrow) to be detected with MRI. Adapted from Shaffer et al 2020, Fordham et al 2021 (Fordham et al., 2021; Shaffer et al., 2020) and Labster theory pages (https://theory.labster.com/nmrspectroscopy/).

Functional magnetic resonance imaging (fMRI) can be used to indirectly measure the net neuronal activity of brain regions trough blood oxygen level dependent (BOLD) contrast imaging. BOLD signal is based on the different magnetic properties of oxyhemoglobin and deoxyhemoglobin which can be detected with fMRI. Neuronal activity increases the regional blood supply and level of oxygenated versus deoxygenated hemoglobin and can hence be indirectly measured with fMRI (Ogawa et al., 1990).

Positron emission tomography (PET) measures ionizing radiation of beta-decaying radioligands injected to the circulation and transported to the target tissues, including the brain. Unstable isotopes, such as carbon-11, emit positrons that collide with surrounding electrons and cause annihilation of the particles. The annihilation releases electromagnetic energy in a form of gamma rays that can be detected with PET scanners as two equivalent 511 keV photons traveling in opposite directions. The selected molecules of interest are labeled with these isotopes to form a radioligand. PET images reflect spatial distribution of radioligand accumulation or presence and allow assessment of the molecule binding to the target tissue (**Figure 2**). Radioligands can be used to measure for instance neurotransmitter synthesis and transmission or the availability of the neurotransmitter receptors (Basu et al., 2011; Kanthan et al., 2017; Kaur et al., 2020).

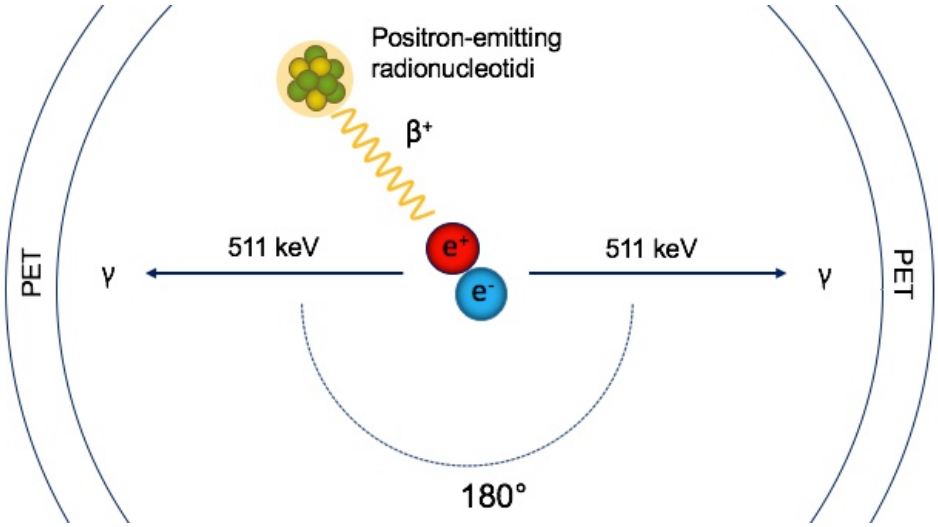


Figure 2. Annihilation of electron and positron into two equivalent 511 keV photons to be detected in PET scanning. Adapted from Verel et al., 2005 (Verel et al., 2005).

To yield biologically meaningful and quantified PET-imaging data, kinetic modelling is needed to take account of the variation in the uptake, washout and retention of radioligand in different tissues and subjects (Lammertsma and Hume, 1996). There exist multiple kinetic models that are appropriate depending on the used radioligand. For example, kinetics of [11C]raclopride and [11C]carfentanil ligands used in the present study can be quantified using the simplified reference tissue model (SRTM). It expresses the radioligand uptake in the tissue of interest relative to the non-displaceable uptake in the reference tissue as binding potential (BP_{ND}) (Innis et al., 2007; Lammertsma and Hume, 1996). Binding potential (BP) refers to the ratio of specifically bound tracer concentration to some reference concentration in equilibrium (Innis et al., 2007). The reference concentration can be defined from blood samples or as non-displaceable uptake from regions not expressing the receptor of interest. Non-displaceable uptake is the sum of the non-specific binding to other than the target molecule and free ligand in the reference tissue (Innis et al., 2007). BP_{ND} in turn, is a ratio of specific and non-displaceable binding in the tissue (1) (Innis et al., 2007). It is in direct relation to the affinity and density of the available of receptors, aka receptor availability (B_{avail}) (2) (Heiss and Herholz, 2006; Innis et al., 2007; Mintun et al., 1984). Only a subset of receptors is available in vivo to bind to radioligand, since some may be compartmentalized in a low affinity state, or occupied by endogenous transmitter (Ariens, 1954; Innis et al., 2007).

(1) $$BP_{ND} = \frac{V_T - V_{ND}}{V_{ND}} = \frac{V_T}{V_{ND}} - 1$$

V_T = total distribution volume of ligand in tissue, V_{ND} = distribution volume of non-displaceable ligand in tissue.

$$BP_{ND} = \frac{f_{ND} B_{avail}}{K_D} \quad (2)$$

f_{ND} = free fraction of the radioligand in the non-displaceable compartment, B_{avail} = density of receptors available to bind radioligand in vivo (receptor availability), K_D = dissociation constant, $1/K_D$ = affinity of the radioligand.

2.2. Structural imaging of social cognition

Brain regions related to social cognition encompass large-scale cortical and subcortical networks. Traditionally in historical lesion studies the social brain has comprised of areas involved in perception and processing of faces (somatosensory and temporal cortices), attribution of emotion (amygdala) and executive functions (prefrontal cortex) (Fernández et al., 2018).

Studies on stroke and other brain damage studies have shown that ToM deficits are associated with lesions in the prefrontal cortex (PFC) and more precisely to ventromedial prefrontal cortex (vmPFC), orbitofrontal (OFC) and frontal pole (Hogeveen et al., 2016; Martín-Rodríguez and León-Carrión, 2010; Szczepanski and Knight, 2014). These social cognition impairing lesions are lateralized mainly to the non-dominant side of the brain (Adams et al., 2019). White matter tracks and the structural connectivity of the brain can be measured by diffusion tensor imaging technique (DTI) exploiting the variable diffusion of water molecules in different tissues (grey and white matter, cerebrospinal fluid) (Soares et al., 2013). Cingulum and arcuate fasciculus have been established as the main white matter tracts associated with to ToM in structural white matter studies (Y. Wang et al., 2018).

Impaired empathy is associated with lesions in OFC, frontal pole, inferior frontal gyrus, ventrolateral prefrontal cortex (vlPFC), insula (INS), temporal pole and also temporo-parietal junction (TPJ) (Hogeveen et al., 2016; Leigh et al., 2013; Shamay-Tsoory et al., 2009; Szczepanski and Knight, 2014). Affective empathy is linked to lesion in IFG, INS, vlPFC and TPJ, whereas cognitive empathy relates more to OFC and frontal pole (Hogeveen et al., 2016; Shamay-Tsoory et al., 2009). In structural white matter studies, empathy has been associated with inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and three limbic tracts; uncinated fasciculus, anterior thalamic radiations and fornix (Y. Wang et al., 2018).

Impaired recognition of emotional expressions has been associated with lesions in the OFC, amygdala, anterior cingulate cortex (ACC), vmPFC, anterior INS (aINS) and somatosensory cortex (Hogeveen et al., 2016; Szczepanski and Knight, 2014). Recognition of fear from faces is impaired following bilateral lesions of amygdala (Kirsch et al 2005), while impaired learning of faces has been associated with lesions to hippocampus and amygdala (Kirsch, 2006). Self-perception and

emotional awareness have been associated with lesions to the frontotemporal cortex, ACC and vmPFC, whereas challenges in recognizing one´s emotions called alexithymia, has been associated to lesions in aINS. These social perception related lesions also seem to be lateralized to the non-dominant side of the brain (Adams et al., 2019). Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and superior longitudinal fasciculus have been presented as the white matter tracts associated also with face processing in structural white matter studies (Y. Wang et al., 2018).

Regulation of social behavioral has been associated mainly to the PFC in studies with patients with stroke and other types of brain damage (Hogeveen et al., 2016; Szczepanski and Knight, 2014), while studies with healthy subjects have found that PFC volume is positively correlated with executive functions (Yuan and Raz, 2014). Dorsolateral prefrontal cortex (dlPFC) is associated with planning, problem solving, rule learning and task-switching behavior (Szczepanski and Knight, 2014). Along with ACC, dlPFC is also related to motivation and attention aspects of behavior regulation (Szczepanski and Knight, 2014). Impaired behavioral inhibition is related to lesions in OFC and vlPFC (Beer et al., 2006; Szczepanski and Knight, 2014), whereas OFC and ACC lesions are associated with poor emotion regulation and decision making (Szczepanski and Knight, 2014; Viskontas et al., 2007). Finally, reactive aggression has been associated to the brain threat circuitry formed by amygdala, hypothalamus and periaqueductal grey in animal and human studies (Bertsch et al., 2020; Feltes and De Boer, 2021) while proactive aggression on its behalf is associated with lower volume of amygdala and aberrancies in the structure of AAC (Belfry and Kolla, 2021).

Taken together, lesion studies have shown that PFC and temporal areas are structurally involved in all four domains of social cognition largely with a lateralization to the non-dominant side of the brain. Empathy and social perception are also linked to limbic and para-limbic structures that are further connected with parietal and somatosensory areas (**Figure 3**).

2.3. Functional imaging of social cognition

Meta-analyses on fMRI studies during social cognition tasks suggest that ToM and mentalizing abilities are associated with TPJ and medial prefrontal cortex (mPFC and especially dorsomedial prefrontal cortex (dmPFC) (Arioli et al., 2021b; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle, 2009; van Veluw and Chance, 2014, 2014; Xiao et al., 2017). Meta-analyses have also indicated precuneus, PCC and temporal lobe as areas with significant role in social processing and ToM (Arioli et al., 2021b; Arioli and Canessa, 2019; van Veluw and Chance, 2014). Resting-state fMRI (rs-fMRI) studies measuring spontaneously fluctuating low-frequency BOLD-signals in task-free situation have reported strong functional connectivity (i.e. correlation of activation time series) within these brain networks (Smitha et al., 2017; van den Heuvel and Hulshoff Pol, 2010). The respective

network is called a default mode network (DMN) or mentalizing network that contributes to social cognitive functions such as autobiographical processing, introspection, mentalizing, ToM and emotional processing (Mars et al., 2012; Padmanabhan et al., 2017; Schilbach et al., 2008; Smitha et al., 2017). TPJ encompasses areas of the posterior superior temporal sulcus (pSTS) and inferior parietal lobule (IPL) which are involved in identification and representation of agency and goals of the perceived action (Amodio and Frith, 2006; Blakemore, 2012; Henry et al., 2016). A recent meta-analysis presented overlapping associations of both affective and cognitive ToM to TPJ and precuneus, whereas affective ToM alone was associated with middle temporal gyrus and cognitive ToM to temporal pole and inferior temporal gyrus.

FMRI meta-analyses have shown that the brain basis of empathy relates most clearly to the dorsal ACC, aINS, anterior mid-cingulate cortex (MCC), TPJ and supplementary motor area (SMA) (Arioli et al., 2021a, 2021b; Chen et al., 2022; Fallon et al., 2020; Fan et al., 2011). In a meta-analysis by Fan et al., emotional empathy was associated with aINS and anterior MCC was associated with the cognitive empathy (Fan et al., 2011).

A meta-analysis of fMRI studies published in 2019 presented IFG, ventral premotor cortex, precentral gyrus, inferior and superior parietal lobule and intraparietal sulcus as the most prominent social perception related areas (Arioli and Canessa, 2019). An earlier meta-analysis on observation and imitation tasks had reported activation of the dorsal premotor cortex, SMA, IPL, primary somatosensory cortex, superior parietal and intraparietal cortex, posterior middle temporal gyrus, fusiform in relation to observation (Caspers et al., 2010). In fMRI meta-analyses, face processing has been most constantly associated with fusiform gyrus, occipital gyrus, inferior frontal gyrus and amygdala (Fusar-Poli et al., 2009; X. Liu et al., 2021; Mende-Siedlecki et al., 2013), while processing of the body in social context has been more related to lateral occipito-temporal cortex areas that are functionally connected with the cerebellum (Downing et al., 2001; Grosbras et al., 2012; Van Overwalle et al., 2015). In turn the processing of emotional vocal expressions has been associated to superior temporal sulcus (STS) and primary auditory cortex in fMRI meta-analyses (Frühholz and Grandjean, 2013; Mauchand and Zhang, 2023; Schirmer, 2018).

Whereas lesion studies have demonstrated the fundamental role of PFC in social behavior, fMRI meta-analyses have presented much wider range of brain areas involved in related processes. Executive functions in general have been associated with ACC, MCC, frontal gyrus, vlPFC, dlPFC, preSMA, SMA, parietal regions, INS, putamen, and angular gyrus (Ardila et al., 2018; Brandl et al., 2019; Hung et al., 2018; Kohn et al., 2014; Xiao et al., 2017; Zhang et al., 2017). More precisely inhibition and impulse control associate broadly to INS, ACC, SMA, preSMA, frontal gyrus, dlPFC, vlPFC, parietal regions and basal ganglia (Brandl et al., 2019; Hung et al., 2018; Mattavelli et al., 2024; Zhang et al., 2017), whereas cognitive

flexibility is associated with fronto-parietal and cingulo-opercular areas (Chuikova et al., 2025). Cognitive emotion regulation is related to vlPFC, dlPFC, pre-SMA (Brandl et al., 2019; Hung et al., 2018; Kohn et al., 2014), whereas reward control is related to the striatum, frontal gyrus, SMA, INS, ACC, PCC, IPL, and PFC (Brandl et al., 2019; Bzdok et al., 2013; Jauhar et al., 2021; Liu et al., 2011).

To give another example of behavioral manifestation of social cognitive functioning, reactive aggression is related to hyperactive processing of arousal and emotions in the amygdala and deficient prefrontal emotion regulation and fronto-parietal inhibitory control (dlPFC, dmPFC, medial OFC, vmPCF, and IPL) (Belfry and Kolla, 2021; Bertsch et al., 2020; Feltes and De Boer, 2021). Proactive aggression in turn is associated with reduced activity in the amygdala and aberrant functioning of the DMN (Belfry and Kolla, 2021).

Altogether, functional imaging studies have shown association between ToM and DMN activity. Empathy in turn, is associated with activity in the cingulate and INS, as well as SMA. Social perception and behavior on their behalf have more widespread connections to large-scale brain networks ranging from fronto-parietal and somato-motor areas to striatal and limbic/paralimbic areas (**Figure 3**).

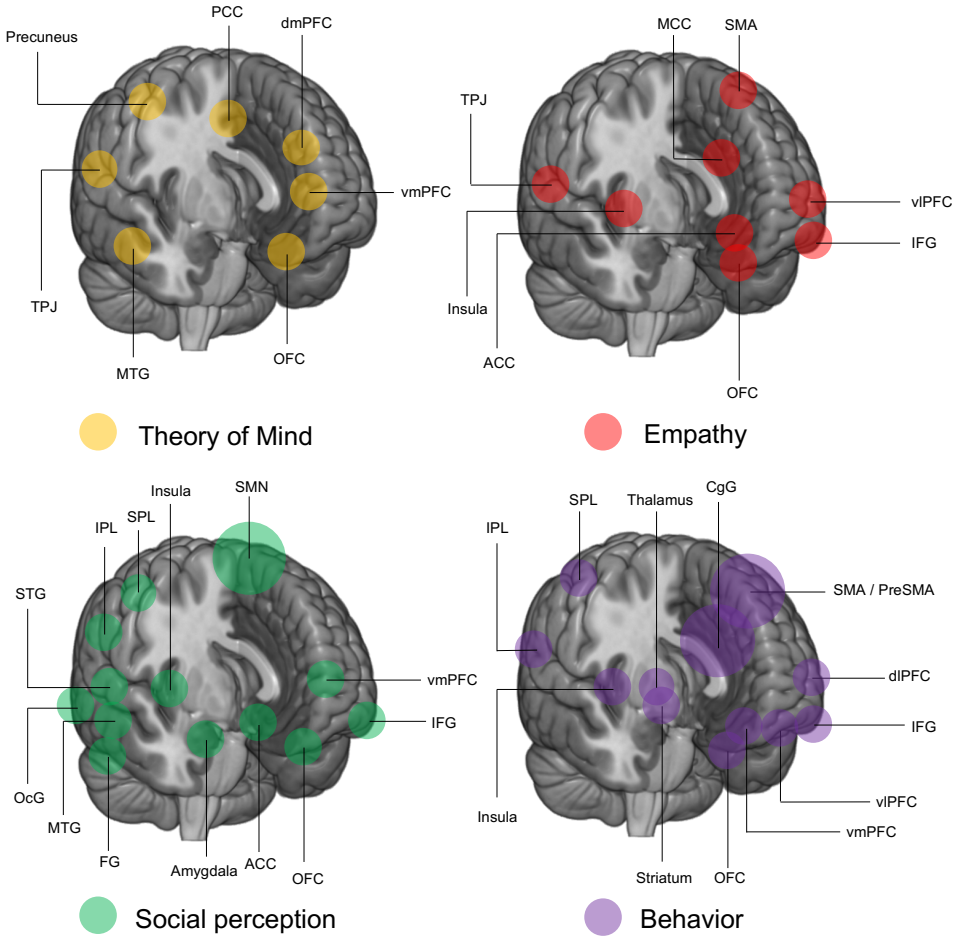


Figure 3. Overview of the brain areas related to the four dimensions of social cognition based on repeated findings in MRI studies (Adams et al., 2019; Beer et al., 2006; Hogeveen et al., 2016; Kirsch, 2006; Leigh et al., 2013; Martín-Rodríguez and León-Carrión, 2010; Shamay-Tsoory et al., 2009; Szczepanski and Knight, 2014; Yuan and Raz, 2014) and fMRI meta-analyses (Ardila et al., 2018; Arioli et al., 2021a, 2021b; Arioli and Canessa, 2019; Brandl et al., 2019; Bzdok et al., 2013; Caspers et al., 2010; Chen et al., 2022; Eres et al., 2018; Fallon et al., 2020; Fan et al., 2011; Frühholz and Grandjean, 2013; Fusar-Poli et al., 2009; Grosbras et al., 2012; Hung et al., 2018; Jauhar et al., 2021; Kohn et al., 2014; M. Liu et al., 2021; Liu et al., 2011; Mattavelli et al., 2024; Mauchand and Zhang, 2023; Mende-Siedlecki et al., 2013; Molenberghs et al., 2016; Schirmer, 2018; Schurz et al., 2014; Van Overwalle, 2009; Van Overwalle et al., 2015; van Veluw and Chance, 2014; Xiao et al., 2017; Zhang et al., 2017).

2.4. Molecular imaging of social cognition

Dopamine, endogenous opioids, oxytocin and serotonin are four main interrelated neurotransmitter systems modulating human social cognition (Barchi-Ferreira and Osório, 2021; Duerler et al., 2022; Han et al., 2021; Kyte et al., 2020; Skuse and Gallagher, 2009; Walsh et al., 2023). The role of other neurotransmitters such as GABA, glutamate and noradrenalin in social cognition is still more unclear (Lam et al., 2006; Marotta et al., 2020; Terbeck et al., 2016).

2.4.1. Dopamine system

Dopamine is a catecholamine neurotransmitter released from the ventral tegmental area, which projects to the PFC and nucleus accumbens (NAcc) of the ventral striatum, forming the mesocorticolimbic circuit that controls reward and motivated behavior (Pavăl and Miclutia, 2021; Reynolds and Flores, 2021). Dopamine released from substantia nigra pars compacta, in turn, projects to the dorsal striatum, forming the nigrostriatal pathway, controlling goal-directed and habitual behavior (Pavăl and Miclutia, 2021). Dopamine receptors are divided into two main groups D1- (D1R, D3R) and D2-receptors (D2R, D4R, D5R), of which D1R and D2R moderate locomotion, reward, reinforcement, learning, and memory. D1R are expressed as postsynaptic receptors widely across the brain and especially in the striatum (Jones-Tabah et al., 2022; Mandic-Maravic et al., 2022), while D2R is additionally expressed also as presynaptic auto-receptors, which modulate dopamine release in the synapses (Soares-Cunha et al., 2016).

According to animal studies, dopamine mediates social reward (Preston, 2017; Sato et al., 2023; Zablocki-Thomas et al., 2022) and is associated with co-operative, altruistic, pair bonding and maternal behavior (Skuse and Gallagher, 2009). It also relates to social dominance, stress, and decision making along with aggressive behavior (Padilla-Coreano and Martínez-Rivera, 2025; Seo et al., 2008). Long term pain bonding has been associated with increased D1R binding in PET imaging studies of monkeys (Hostetler et al., 2017; Zablocki-Thomas et al., 2022). Dopaminergic system has also a role in the cognitive flexibility and stability which is thought to be mediated by the tonic and phasic modes of dopamine release—tonic dopamine is thought to be associated with the stabilization and maintenance of PFC representations, and phasic dopamine is associated with the updating of these representations (Grace et al., 2007; Zweifel et al., 2009).

In humans, the use of dopaminergic agents, such as cocaine and methamphetamine, is associated with smaller social networks and impaired emotion recognition and emotional empathy (Quednow, 2017). These dopaminergic agents also increase impulsivity in children without Attention-Deficit/Hyperactivity Disorder (ADHD) and they are linked with aggressive social behavior (Seo et al., 2008). In addition, cocaine users present difficulties in the ToM (Hulka et al., 2014; Preller et al., 2014b) and display diminished emotional

engagement and reward in social interaction (Preller et al., 2014a; Tobler et al., 2016). On the other hand, antipsychotic dopamine antagonists reduce aggressive behavior and impair the ability to recognize angry faces in humans (Seo et al., 2008). Human PET-imaging studies have associated impulsive behavior and reward processing with striatal dopaminergic functioning in healthy human volunteers (Buckholtz et al., 2010b; Dubol et al., 2018; Kim et al., 2014; Weiland et al., 2014). A PET-imaging study by Schluter et al. showed that the level of dopamine synthesis in the midbrain was negatively correlated with aggressive behavior in neurotypical males (Schlüter et al., 2013). In turn, higher dopamine release in amygdala has been associated with maternal bonding with the child (Atzil et al., 2017), whereas higher release in medial OFC and mPFC has been associated to human romantic love in human PET-imaging studies (Takahashi et al., 2015). Finally, dopamine receptor D2 gene variants have been found to regulate empathy responses, agreeable behavior, social adjustment and degree of attachment (Han et al 2021).

2.4.2. Opioid system

The endogenous opioid system controls a wide variety of functions, from basic homeostasis and anti-nociception to emotions, social attachment, and reward (Machin and Dunbar, 2011; Nummenmaa et al., 2015; Nummenmaa and Tuominen, 2018; Rocchi et al., 2020; Turtonen et al., 2021). Beta-endorphin is a neuropeptide released from hypothalamic nuclei and mesolimbic structures, projecting to other hypothalamic and corticolimbic structures, frontal lobes, brainstem, and periaqueductal grey (Machin and Dunbar, 2011; Rocchi et al., 2020). Beta-endorphin binds to three different opioid receptors, mu- (MOR), delta- (DOR), and kappa- (KOR), which are differentially distributed across the cortical and subcortical areas. Opioid receptors are widely expressed in the brain as postsynaptic receptors, but also as modulatory presynaptic auto-receptors (Reeves et al., 2022).

Since the late seventies, opioid system has been proposed to be linked with social attachment. In animals, endogenous opioids modulate social bonding, separation anxiety and play (Adolphs, 2001) and mu-opioid agonists also influence the social approach and withdrawal behavior depending on the dose, duration of dosing, and the social context (Pellissier et al., 2018).

Clinical studies in humans have shown that opiate addicts in maintenance treatment display deficits in social inference, emotion recognition and ToM (Eidenmueller et al., 2021; Gandolphe et al., 2018; McDonald et al., 2013; Yazgeç et al., 2023). Opioid receptor mu 1 gene (OPMR1) variant is also associated with ability to blend into social networks in humans (Han et al., 2021). Moreover, human PET-studies have associated higher MOR binding to prosocial behavior, such as social laughter, social touch, secure attachment style and vicarious pain but also to

impulsive behavior (Karjalainen et al., 2017, 2016; Love et al., 2009; Manninen et al., 2017; Nummenmaa et al., 2016, 2015; Turtonen et al., 2021).

2.4.3. Oxytocin system

Oxytocin is hormone effecting the female reproductive system, but also a key neurotransmitter associated with human social behavior. In animal studies oxytocin has been associated with affiliate behavior, social memory and social reward (Adolphs, 2001; Barchi-Ferreira and Osório, 2021; Walsh et al., 2023). Human studies in turn have presented evidence on its role in affiliate and altruistic behavior, ToM, empathy, trust and social fear (Barchi-Ferreira and Osório, 2021; Florea et al., 2022; Han et al., 2021; MacDonald and MacDonald, 2010; Stark et al., 2023).

2.4.4. Serotonin system

Serotonin is a monoamine neurotransmitter regulating body homeostasis system, emotion, reward and social behavior (Duerler et al., 2022; Ligneul and Mainen, 2023). Serotonin functioning is linked to social dominance, integration and reward in primate animal studies (Adolphs, 2001; Krakowski, 2003; Sato et al., 2023; Walsh et al., 2023). Decreased serotonin activity increases aggressive and impulsive behavior, while elevated serotonin levels reduce aggression, improve impulse control and increase cooperative behavior in humans and animals (Duerler et al., 2022; Krakowski, 2003; Seo et al., 2008; Ziomkiewicz-Wichary, 2016). Human studies have also associated serotonin with integration of social information, value-based decision making, sensitivity to social factors, cognitive flexibility, fear learning and empathy (Duerler et al., 2022; Olami and Peled-Avron, 2024; Schmid and Bershad, 2024; Tortora et al., 2023; Walsh et al., 2023).

2.4.5. Interregulatory neurotransmitter connections

These four core neurotransmitter systems of social cognition described above are interconnected and constitute a complex inter-regulatory network. Oxytocin regulates dopamine and serotonin release which promotes its prosocial effects, but it has also interaction with endogenous opioid system in modulating social behavior (MacDonald and MacDonald, 2010; McCall and Singer, 2012; Putnam and Chang, 2022; Sato et al., 2023; Walsh et al., 2023). Evidence from animal studies and human PET studies suggests a complex but positive interrelationship between the dopamine and opioid regulation (Colasanti et al., 2012; Escobar et al., 2020; Majuri et al., 2018; Margolis et al., 2014; Mick et al., 2014; Rada et al., 2010; Wiskerke et al., 2011). Their interaction is critical for social motivation and reward processing (Kohls et al., 2012; Vanderschuren et al., 2016). The inhibitory effect of serotonin on dopaminergic system is also well established and their interaction has been

associated, for instance, to impulsive aggression (Di Giovanni et al., 2010; Seo et al., 2008).

2.4.6. Neurochemistry of aggression

The most evident neurotransmitters associated with aggression based on animal and human studies have been serotonin, dopamine and gamma-aminobutyric acid (GABA) (Feltes and De Boer, 2021; Narvaes and Martins de Almeida, 2014; Padilla-Coreano and Martínez-Rivera, 2025; Umukoro et al., 2013; Yanowitch and Coccaro, 2011). Even though animal and human studies have associated especially impulsive aggressive behavior with lower serotonergic and higher dopaminergic functioning (Seo et al., 2008), human PET-imaging studies have thus far established only preliminary or conflicting associations to different serotonin receptor, serotonin transporter, dopamine receptor binding and dopamine synthesis (Feltes and De Boer, 2021; Kolla and Houle, 2019; Yanowitch and Coccaro, 2011). To the best of author´s knowledge there are no PET-imaging studies related to GABA and aggression at the moment.

3. Autism spectrum disorder

ASD is a heterogenous neurodevelopmental disorder with impairments in social communication and restricted repetitive behavior. ASD symptoms emerge in early developmental age from approximately 2 years of age with typical age of diagnosis being 4-5 years of age (Lord et al., 2020). For instance, the difficulties in social communication can appear as limited recognition and use of gestures and facial expressions, lack of interest for others, lack of eye contact and inappropriately loud speech and control of physical distance to other humans (Hirota and King, 2023). Restricted and repetitive behavior can appear as repeated use of words and phrases, stereotypic movements, excessive interest in objects or sensory stimuli and insistence on sameness (Hirota and King, 2023). Other neuropsychiatric disorders such as ADHD and intellectual disability (ID) along with depression, anxiety and sleep problems are common psychiatric co-morbidities in ASD (Hirota and King, 2023; Lord et al., 2020). The clinical manifestation of ASD can range from individuals with ID and severe language impairment to individuals with above average intellectual and language abilities, but difficulties in social communication (Hirota and King, 2023). The prevalence of ASD in Finland and worldwide is estimated to be ca. 0.8 % and it is approximately 4 times higher in male than in female (Delobel-Ayoub et al., 2020; Hirota and King, 2023; Lord et al., 2020). ASD is strongly heritable disorder (64-91%) with a complex genetic background. Environmental risk factors, such as prenatal maternal factors, play role in the etiology of ASD (Tick et al., 2016; Woodbury-Smith and Scherer, 2018).

The term autism was first introduced in the early 20th century by Swiss psychiatrist Eugen Bleuler but then as a symptom of “definite withdrawal from the

external world" in the context of schizophrenia (Verhoeff, 2013). In 1943 child psychiatrist Leo Kanner presented a case series of 11 children with disturbances of affective contact referring to early infantile autism as a distinct disorder of its own (Verhoeff, 2013). Kanner presented the extreme self-isolation and obsessive insistence of preservation of sameness as two primary pathognomonic features of the autism disorder (Verhoeff, 2013). Only a year after Kanner's original case series, a German psychiatrist Hans Asperger presented a case series of four highly recognizable type of children with "disturbance of adaptation in social environment" under the term of autistic psychopathy (Verhoeff, 2013). The term psychopathy was used by Asperger to refer to the antisocial tendencies and lack of empathy in these presented cases, even though there has been no proof of increased criminal convictions (Carthy and Murphy, 2021; Hippler et al., 2010). The children in Asperger´s series developed highly grammatical speech, while Kanner's series demonstrated children with late or no development of language (Verhoeff, 2013). For two decades Kanner's description of the disorder remained as a basis for concepts of autism while Asperger´s publications were not widely recognized for the time being (Verhoeff, 2013).

In the seventies the early psychoanalytic theories of emotionless parenting styles evolved into theories of language deficits as the etiology of autism (Rajendran and Mitchell, 2007). Later on, since the eighties there have been three dominant cognitive theories of autism; 1) defects in the ToM, 2) defects in the executive functions and 3) weak central coherence referring to a cognitive style of focusing more into details instead of the issue as a whole (Rajendran and Mitchell, 2007). However, even integrated together, still these three psychological theories do not explain the broad and heterogenous symptom spectrum of ASD.

The first formal diagnostic criteria for autism, published in 1980 in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) (American Psychiatric Association, 1980), included infantile autism as part of a broader class of pervasive developmental disorders (PDD). This definition followed Kanner's original description assuming severe deficits in social relationships, accompanied by deficits in language or communication, symptom onset before 30 months, and no hallucinations or delusions (Deisinger, 2011; Volkmar and Reichow, 2013). Due to the popularity of Lorna Wing's review article on Hans Asperger´s original case report, the DSM-IV published in 1994 introduced new diagnostic criteria for autistic disorder, but also new diagnosis, Asperger syndrome, where delay in cognitive and language development is not observed (Deisinger, 2011; American Psychiatric Association, 1994). For autistic disorder, DSM-IV required the presence of at least six criteria: two involving social impairment, one pertaining to impaired communication, and one relating to behaviors and interests, as well as an onset before age 3 years, and the exclusion of both Rett syndrome and PDD as possible causes of symptoms (Deisinger, 2011; American Psychiatric Association, 1994). The diagnostic criteria of autistic disorder and the whole

domain of PDDs was also unified with World Health Organization´s International Statistical Classification of Diseases and related health problems 10th revision (ICD-10) classification for worldwide cross-cultural research purposes (Rosen et al., 2021; World Health Organization, 2016). In the latest DSM-V the pervasive developmental disorders class has been replaced with ASD as broad umbrella concept while leaving the previous DSM-IV subgroups Asperger syndrome, Rett syndrome and disintegrative syndrome out of the manual. The latest ICD-11 classification largely follows the DSM-V diagnostic criteria, but with some differences in the section concerning repetitive and restricted behavior section (Greaves-Lord et al., 2022; World Health Organization, 2019). The current diagnostic criteria from DSM-V are presented in **Table 1**.

ASD is a clinical diagnosis usually defined as agreement within a multidisciplinary professional team based on a detailed developmental history and observation of the individual's behaviors using standardized diagnostic tools (Hirota and King, 2023). Diagnostic tools such as Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic interview -revisited (ADI-R) can be used to inform the diagnosis and quantify the autism severity. ADI-R is a standardized, semi-structured, investigator-based interview for caregivers of autistic individuals based on the DSM-IV and ICD-10 diagnostic criteria of autistic disorder. The interview presents separate scores in the areas of communication, social skills, and restricted, repetitive and stereotyped behaviors, as well as early developmental history. It allows the separate quantification of symptom severity in each of these domains, ranging from no definite behavior of the type specified to extreme severity (Lord et al., 1994). The ADOS is a standardized, semi-structured observational assessment for domains of communication, reciprocal social interaction, imagination/creativity and stereotyped behaviors and restricted interests based on the DSM-IV criteria for autism disorder. It includes four different modules for the evaluation of individuals with different developmental and language levels, where module four is used to assess adolescents and adults with fluent language ability (Lord et al., 1989).

Table 1. DSM-5 diagnostic criteria for ASD (American Psychiatric Association, 2022).

Autism Spectrum disorder 299.00

Diagnostic Criteria

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by all of the following, currently or by history:

1. Deficits in social-emotional reciprocity
2. Deficits in nonverbal communicative behaviors
3. Deficits in developing, maintaining, and understanding relationships

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:

1. Stereotyped or repetitive motor movements
2. Insistence on sameness, inflexible adherence to routines
3. Highly restricted, fixated interests
4. Hyper- or hyporeactivity to sensory input

C. Symptoms must be present in the early developmental period

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning

E. These disturbances are not better explained by intellectual developmental disorder

3.1. Structural imaging of ASD

No clear and consistent neuropathology has been found for autism and the cerebral anatomical neuroimaging findings in ASD have been heterogenous (Ecker et al., 2013; Pagnozzi et al., 2018; Riddle et al., 2017). The most consistent structural finding with MRI studies in people with ASD is the enlargement of the total brain volume and cerebrospinal fluid within the first six post-natal years (Mosconi et al., 2006; Pagnozzi et al., 2018; Riddle et al., 2017; Sato and Uono, 2019; Zielinski et al., 2014). The brain surface area and gyrification of the brain has also been reported to be increased in comparison with typically developing individuals (Pagnozzi et al., 2018).

VBM meta-analyses have shown decreased grey matter volume (GMV) in ACC, cerebellum and mPFC but increased GMV in temporal gyri (inferior, middle, superior), frontal gyri (middle, superior) and precentral gyrus as the most recurrent changes in ASD versus controls across age groups (Carlisi et al., 2017; Guo et al., 2024; Lukito et al., 2020). In children the most consistent findings have been decreased GMV in cerebellum and INS and increased GMV in medial frontal gyrus and superior frontal gyrus, angular gyrus and precuneus (Guo et al., 2024; Liu et al., 2017; Lukito et al., 2020). With adults in turn, the most recurring findings have been decreased GMV in ACC, cerebellum, precuneus and mPFC but also increased GMV in medial temporal gyrus and postcentral gyrus (Guo et al., 2024; Yang and Hofmann, 2016).

One of the most prominent neuropathologic theories of ASD suggests that anatomic abnormalities are age-specific (Courchesne et al., 2007; E. Courchesne et al., 2011; Eric Courchesne et al., 2011; Courchesne and Pierce, 2005; Ecker et al.,

2013; Zielinski et al., 2014). The brain undergoes a period of precocious growth of grey and white matter in the early postnatal life of ASD individuals (Eric Courchesne et al., 2011; Rafiee et al., 2022), which is followed by decreased or paused age-related brain growth and accelerated synaptic pruning eliminating unnecessary neural connections (Amaral et al., 2008; Mosconi et al., 2006; Rafiee et al., 2022; Sato and Uono, 2019; Zielinski et al., 2014). The accelerated brain growth in the early childhood is found to correlate with the onset of ASD symptoms and the later decrease of grey and white matter volume has been suggested to mark the severity of ASD symptoms (Rafiee et al., 2022). Moreover, later on in adulthood and older age, there seems to be an acceleration in age-related brain degeneration (Eric Courchesne et al., 2011) This theory has been supported by findings in longitudinal and cross-sectional MRI studies (E. Courchesne et al., 2011; Eric Courchesne et al., 2011).

While the early overgrowth found in volumetric MRI studies of ASD pertains mostly to the frontal and temporal lobes (Amaral et al., 2008; Carper and Courchesne, 2005; Pagnozzi et al., 2018; Riddle et al., 2017), the abnormal age-related degeneration is focused more in the temporal and parietal lobes (Braden and Riecken, 2019; Wallace et al., 2010). Two latest neuroimaging studies with large multinational samples of ASD patients including all age groups from ENIGMA (Enhancing Neuroimaging Genetics Trough Meta-analysis) ASD working group have found support for theories on aberrant growth trajectory leading into thinner temporal cortex and thicker frontal cortex in adulthood (Boedhoe et al., 2020; Van Rooij et al., 2018). MRI and post-mortem studies also support a similar abnormal growth trajectory in the cerebellum, but with the exception of life-long hypoplasia in the vermis areas (Amaral et al., 2008; Pagnozzi et al., 2018).

The pathologic brain overgrowth of the brain seems to be more salient in the white matter than in the grey matter (Amaral et al., 2008; Mosconi et al., 2006; Sato and Uono, 2019). This has raised hypothesis of autism being a network problem of local over connectivity and long distance under connectivity with abnormalities in the connecting fibers (Mosconi et al., 2006; Pagnozzi et al., 2018). This theory is supported by DTI studies with recent meta-analyses showing decreased fractional anisotropy in the corpus callosum, corona radiata and cerebral peduncles (Di et al., 2018; Koshiyama et al., 2020; Rafiee et al., 2022; Zhao et al., 2022).

Taken together the neuroimaging studies suggest that structural deviances in ASD are age-dependent with enlargement of the total brain volume in early childhood being the most consistent finding (Courchesne et al., 2001; Guo et al., 2024; Lukito et al., 2020; Mosconi et al., 2006; Pagnozzi et al., 2018; Riddle et al., 2017; Sato and Uono, 2019; Zielinski et al., 2014). The theory of aberrant frontotemporal growth trajectory resulting in thicker frontal cortex and thinner temporal cortex is supported by longitudinal studies and mega-analyses (Boedhoe et al., 2020; Eric Courchesne et al., 2011; Van Rooij et al., 2018), but structural VBM

meta-analyses have presented conflicting fronto-temporal results (Guo et al., 2024; Lukito et al., 2020). The lower GMV in the cerebellum across all ages is the most congruent finding in the structural VBM studies (Carlisi et al., 2017; Guo et al., 2024; Liu et al., 2017; Lukito et al., 2020; Yang et al., 2016).

3.2. Functional imaging of ASD

Meta-analyses of fMRI studies on ASD have shown altered activation of the social brain areas, somatosensory cortex, striatum and occipital areas in different social and non-social tasks. In task-based and rs-fMRI meta-analyses, there are network level findings of hypoactivation in the executive frontoparietal network and mentalizing network DMN (Carlisi et al., 2017; Di Martino et al., 2009; May and Kana, 2020; W. Wang et al., 2018) Some studies also report altered connectivity and hypoconnectivity within the DMN and sensomotor networks in ASD (Ilioska et al., 2023; Lau et al., 2020, 2019; Liloia et al., 2024; Wang et al., 2021; W. Wang et al., 2018).

Across different types of tasks, hypoactivation of the left amygdala has been a consistent finding in meta-analyses (Goodwill et al., 2023; Tamon et al., 2024). Meta-analyses of specific tasks have shown some variance in their results, but aberrancies in social cognition areas, ACC and STS have stand out as the most coherent findings. Other reported effects in meta-analyses have been more task-specific as overviewed below (**Table 2)**.

3.2.1 Social tasks

In social tasks related to face processing, ToM, and emotion processing, higher activation related to ASD has been found in post- and precentral gyrus, STS and frontal gyrus whereas the activation has typically been lower in ACC, amygdala and frontal gyrus (Di Martino et al., 2009; Dickstein et al., 2013; Goodwill et al., 2023; Patriquin et al., 2016). Face processing tasks have induced hyperactivation in the STS, whereas fusiform gyrus and ACC have been hypoactivated (Aoki et al., 2015; Di Martino et al., 2009; Patriquin et al., 2016; Philip et al., 2012; Sugranyes et al., 2011). ToM tasks have shown hypoactivation of the STS and IPL (Philip et al., 2012; Sugranyes et al., 2011). One meta-analysis found higher activation in the medial frontal gyrus and IFG, IPL, precentral gyrus during observation/imitation task when activation was lower in medial and inferior temporal gyrus, inferior and medial occipital gyrus and postcentral gyrus in ASD (Yang and Hofmann, 2016). Two meta-analyses on social reward tasks in ASD have presented lower activation of the striatum, but other findings were controversial or have not been replicated (Clements et al., 2018; Janouschek et al., 2021).

3.2.2. Non-Social tasks

Meta-analyses suggest that in non-social tasks the individuals with ASD show consistent hyper-activation of ACC (Di Martino et al., 2009; Dickstein et al., 2013). During executive tasks, individuals with ASD in turn have higher activation of ACC and PFC (Di Martino et al., 2009; Philip et al., 2012), while inhibitory control tasks have shown lower activation of ACC, dlPFC and IPL but also higher activation in inferior occipital cortex (Carlisi et al., 2017; Lukito et al., 2020). Lower activation of the striatum but also ACC has been found in non-social reward tasks of ASD meta-analyses (Clements et al., 2018; Janouschek et al., 2021).

Table 2. Overview of the task-based fMRI meta-analyses in ASD. Areas with higher or lower fMRI activation in at least two meta-analyses are included in the table, excluding areas with contradictory findings (Aoki et al., 2015; Carlisi et al., 2017; Clements et al., 2018; Di Martino et al., 2009; Dickstein et al., 2013; Goodwill et al., 2023; Guo et al., 2024; Janouschek et al., 2021; Lukito et al., 2020; May and Kana, 2020; Nickl-Jockschat et al., 2011; Patriquin et al., 2016; Philip et al., 2012; Sugranyes et al., 2011; Tamon et al., 2024; Yang and Hofmann, 2016).

Social tasks			Non-social tasks		
Social	Post/PreCG STS Frontal gyrus	↑	Non-social	ACC	↑
	ACC Amygdala Frontal Gyrus	↓		-	↓
Face processing	STS	↑	Inhibitory control	IOC ACC	↑
	ACC FFA	↓		IPL dlPFC	↓
Theory of mind	-	↑	Executive functioning	ACC PFC	↑
	STS IPL PFC	↓		-	↓
Social reward	Insula Putamen STS FFA	↑	Non-social reward	-	↑
	Caudate ACC Hipp LOC IFG	↓		Nacc Caudate ACC	↓
Observation, imitation	MFG IFG IPL PreCG	↑	Restricted interest reward	Caudate Nacc Insula Putamen	↑
	ITG MTG MOG IOG PostCG	↓		NAcc ACC	↓

3.3. Molecular imaging of ASD

Aberrancies in different neurotransmitter functioning have been proposed to underlie ASD, but human studies have yielded only limited evidence for any specific systems. Since dopamine, endogenous opioid and serotonin systems are central to social cognition they also play an important role in the neurotransmitter imaging of ASD (Lam et al., 2006; Marotta et al., 2020; Tan et al., 2022). Currently there are no reliable PET-imaging tracers for oxytocin system in human brain imaging (Beard et al., 2018; Wenzel et al., 2016).

3.3.1. Dopamine system

Animal and human genetic studies have variably supported for both increased and decreased dopamine regulation in ASD compared to neurotypical (Blum et al., 2024; Fuccillo, 2016; Kosillo and Bateup, 2021). Animal studies have presented dysfunction of the dopaminergic mesocortocolimbic circuits and suggested a decreased social reward and motivation in ASD (Chevallier et al., 2012; Fuccillo, 2016; Kosillo and Bateup, 2021; Pavăl and Miclutia, 2021). Reduced activation of the dopaminergic striatal areas during reward processing has been associated with ASD in human fMRI studies and further support these theories (Clements et al., 2018; Hsu et al., 2018a; Kohls et al., 2012; Neufeld et al., 2019). Human positron emission tomography (PET) studies have further found deviant dopamine signaling in ASD compared to controls, but the study methods and results have been heterogenous (Tan et al., 2022; Zürcher et al., 2015). The striatal dopamine has been shown to play a role also in repetitive behavior of animals, but human studies have not been conclusive and connections to ASD have remained weak (Fuccillo, 2016; Langen et al., 2011a, 2011b). Finally, dopamine antagonist medications such as risperidone and aripiprazole may alleviate autism symptoms, including irritability and stereotypic behavior (Mandic-Maravic et al., 2022; Marotta et al., 2020; Pavăl, 2017; Pavăl and Miclutia, 2021).

3.3.2. Opioid system

Since the late seventies, opioid system dysfunctions have been proposed to be linked with autism (Kyte et al., 2020; Machin and Dunbar, 2011; Panksepp, 1979; Sahley and Panksepp, 1987), and more recently, MOR knock-out mice were shown to manifest autism-related behaviors (Oddi et al., 2013). Whereas opioidergic agents influence the social motivation and social cognition in humans, opioid antagonists may reduce hyperactivity and restlessness symptoms in ASD (Eidenmueller et al., 2021; Gandolphe et al., 2018; Marotta et al., 2020; McDonald et al., 2013; Roy et al., 2015). PET imagin studies have associated endogenous opioid system to modulation of social behavior in humans, but there are no previous

studies related to ASD (Karjalainen et al., 2016; Manninen et al., 2017; Nummenmaa et al., 2016, 2015).

3.3.3. Serotonin system

Elevated levels of serotonin have been associated with ASD in animals and humans ever since the sixties and it has been the most commonly studied neurotransmitter in vivo ASD research (Lam et al., 2006; Marotta et al., 2020; Tan et al., 2022; Zürcher et al., 2015). The human PET-imaging studies have presented age dependent findings of lower and asymmetric synthesis of serotonin in children with ASD, suggesting a deviant developmental trajectory of serotonin system in ASD (Ryu and Oh, 2025; Tan et al., 2022; Zürcher et al., 2015). There are also findings of lower serotonin transporter level and receptor density in ASD, but studies with different tracers have presented conflicting results (Tan et al., 2022; Zürcher et al., 2015).

3.3.4. Other transmitter systems

Only a few studies with small sample size have utilized PET-imaging with GABA and glutamate receptor tracers in ASD and the results remain controversial (Tan et al., 2022). There is only one PET-imaging study focusing on the noradrenalin system in ASD and it presented no differences in ASD group compared to controls (Kubota et al., 2020).

4. Psychopathy

The term psychopathy has been used in the European psychiatric and psychopathologic literature ever since the early 1800s as a broad term referring to pathology of the psyche. The term was not specifically used in the context of personality disorder characterized by antisocial and criminal behavior, until German psychiatrists Koch, Kraepelin and Schneider in the early decades of 20th century. It was finally the description of 21 essential characteristics of psychopathic personality disorder based on the nine case studies in the book The Mask of Sanity by an American psychiatrist Harvey Cleckley in 1941 that set the basis for our modern understanding of psychopathy (Horley, 2014). After ten years of the Cleckley's definitions on psychopathy, the American Psychiatric Association (APA) introduced the first DSM-I criteria with a diagnosis of sociopathic personality disturbance including previous terms of psychopathic personality and constitutional psychopathic state (Crego and Widiger, 2015; American Psychiatry Association, 1952). Based on studies by L. Robins, this definition was systematized and narrowed down to nine criteria with requirement for childhood conductance disorder in 1980 DSM-III-R diagnosis for antisocial personality disorder (Crego and Widiger, 2015; American Psychiatric Association, 1987).

Psychopathy is a serious disorder of social cognition characterized by grandiosity, manipulativeness, disinhibited, egoistic and callous unemotional traits (Cooke and Michie, 2001; De Brito et al., 2021a). It has not been a formal diagnosis in the DSM- or ICD-classifications, but the traits have been part of the antisocial and asocial personality disorder diagnostic criteria (Crego and Widiger, 2015; Jantzi and Moulin, 2025; World Health Organization, 2016, 2019). Psychopathy is regarded as a specifier for antisocial personality disorder, which is also mentioned in the emerging alternative diagnostic criteria models -section of DSM-V (Raine, 2018; American Psychiatric Association, 2022). Callous unemotional traits refer to a lack of guilt, empathy, and concern about poor performance in important activities. Together with shallow/deficient affect, they constitute the core affective facets of adult psychopathy (De Brito et al., 2021a). Conduct disorder with callous unemotional traits (CD/CU) in children has been proposed as a possible precursor for psychopathy (De Brito et al., 2021a; Raine, 2018). In the current DSM-V criteria, antisocial personality disorder is based on the diagnosis of conduct disorder before the age of 15 years and continuous antisocial behavior from the age of 15 until age of 18 years and thereafter (**Table 3**). The antisocial behavior is evaluated based on seven maladaptive traits (American Psychiatric Association, 2022). The DSM-V specifier for psychopathy includes the lack of anxiousness and fear capturing the stress immunity, and low social withdrawal and high attention seeking capturing the social potency of psychopathy (Crego and Widiger, 2015; American Psychiatric Association, 2022). The DSM-V also includes a specifier of "limited prosocial emotion" for conduct disorder referring to callous unemotional traits (Salekin, 2016; American Psychiatric Association, 2022).

Table 3. DSM-5 criteria for antisocial personality disorder (American Psychiatric Association, 2022).

Antisocial personality disorder 301.7

Diagnostic criteria

A. A pervasive pattern of disregard for and violation of the rights of others, occurring since age 15 years, as indicated by three (or more) of the following:

1. **Failure to conform to social norms with respect to lawful behaviors, as indicated by repeatedly performing acts that are grounds for arrest**
2. **Deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure**
3. **Impulsivity or failure to plan ahead**
4. **Irritability and aggressiveness, as indicated by repeated physical fights or assaults**
5. **Reckless disregard for safety of self or others**
6. **Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations**
7. **Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another**

B. The individual is at least 18 years old

C. There is evidence of conduct disorder with onset before age 15 years

D. The occurrence of antisocial behavior is not exclusively during the course of schizophrenia or bipolar disorder

Psychopathy is strongly associated with violence and criminal recidivism (Junewicz and Billick, 2020; Murrie et al., 2004). In addition to antisocial personality disorder, other cluster B personality disorders such as narcissistic and borderline personality disorders along with substance use disorder and ADHD are common psychiatric co-morbidities of psychopathy (De Brito et al., 2021a). While the prevalence of psychopathy is estimated to be around 1 % in general population, the prevalence can exceed 25% in prisoners and was reported to be 16.4% in Finnish incarcerated offenders (De Brito et al., 2021a; Jüriloo et al., 2014). Psychopathy is strongly heritable (Blonigen et al., 2005; Larsson et al., 2006; Tuvblad et al., 2017, 2014), but the exact genetic factors are still unknown (De Brito et al., 2021a). Environmental factors such as prenatal maternal stress, childhood maltreatment and negative parenting styles also play a role in the development of psychopathy, but these are at least partly entangled and interact with the predisposing parental genetic factors (De Brito et al., 2021a).

The theories on psychopathy have been developing into two main directions with the emotion-focused stressing on the dysfunction of the affective system and attention-focused stressing on broader information processing deficits that are not specific to emotions. The first theory of low-fear in psychopathy was proposed by Lykken in 1957 and has been followed by Blair's amygdala centered theory of Integrated Emotion System in 2005 and Kiehl's Paralimbic Dysfunction Hypothesis in 2006 (Blair, 2005b; Hamilton et al., 2015; Kiehl, 2006). One of the most known attention-based theories of psychopathy is the Response Modulation Hypothesis, which proposes a limitation in the ability to use contextual information that contraindicates goal-related behavior and results in failure to stop and reflect on the potentially maladaptive behavior (Hamilton et al., 2015). The latest theories of Differential Amygdala Activation model by Mould, Killcros and Dadds (2012) and Impaired Integration model by Hamilton et al. (2015) try to combine the affective and cognitive view on psychopathy based on the findings of fMRI studies (Hamilton et al., 2015; Moul et al., 2012). Differential Amygdala Activation model is based on the idea of dysfunction in the reflexive and preconscious shift of attention to salient stimuli, such as fear due to reduced activation of the basolateral amygdala (Hamilton et al., 2015). In turn the Impaired Integration model proposes that, the psychopathic syndrome can be understood as inadequate perceptual ability to integrate socio-emotional information from different components, such as memory, attention, cognition and emotions due to poor connectivity between functional neural networks (Hamilton et al., 2015).

In the 1970s a Canadian psychologist Robert Hare adopted Cleckley's theories as a basis to develop a clinical tool, 22-item Psychopathy checklist (PCL), for assessing psychopathy in individuals. Whereas the PCL measured more the personality traits and was validated and greatly used in forensic settings, the DSM-III focused more on the criminal antisocial behavior and served the work at the psychiatric clinics (Crego and Widiger, 2015). Ever since the DSM-IV in 1991, the

diagnostic criteria of antisocial personality disorder have moved towards the direction of PCL and brought the two related concepts, antisocial personality disorder and psychopathy closer to each other (Crego and Widiger, 2015).

Hare's revisited version of PCL in 1991 (PCL-R) divides psychopathy into two main factors: interpersonal/affective factor 1 and chronic antisocial lifestyle factor 2 (Hare, 2011). The factor 1 is further divided to interpersonal and affective facets and factor 2 is divided to lifestyle and antisocial facets **(Table 4**). Each of these 20 facets are scored in a 3-point scale from 0 to 2 with a total score cut-off limit of 30 out of 40 for psychopathy (Brazil, 2016; Neumann et al., 2013). In the Scandinavian countries the PCL-R cut-off limit for psychopathy has been suggested to be lower than the original North American one, being in the range of 25–26 (Jüriloo et al., 2014). The term primary psychopathy refers to these factor 1 facets of psychopathy, which are seen as the core of psychopathy resulting largely from genetic and biological influences (Crego and Widiger, 2015; Verschuere and te Kaat, 2020; Yildirim and Derksen, 2015b). Secondary psychopathy in turn refers to sociopathic and social deviance of factor 2 facets, which are related to adverse environmental factors such as developmental trauma or maltreatment (Verschuere and te Kaat, 2020; Yildirim and Derksen, 2015b). Primary psychopathy is associated with increased emotional stability, fearlessness and being more self-assured than secondary psychopathy, which is often associated with greater psychopathology (De Brito et al., 2021a; Maguire et al., 2024). Today, the PCL-R is still the most validated technique in the forensic settings to evaluate psychopathy (Horley, 2014).

Table 4. Psychopathy Checklist Revisited facets (Hare, 2011).

Psychopathy Checklist - Revised

- **Factor 1**

Interpersonal
- Glibness – superficial charm
- Grandiose sense of self-worth
- Pathological lying
- Conning – manipulative

Affective
- Lack of remorse or guilt
- Shallow affect
- Callous – lack of empathy
- Failure to accept responsibility

Factor 2

Lifestyle
- Need for stimulation
- Parasitic lifestyle
- Lack of realistic, long-term goals
- Impulsivity
- Irresponsibility

Antisocial
- Poor behavioural control
- Early behavioural problem
- Juvenile delinquency
- Revocation of conditional release
- Criminal versatility

4.1. Structural imaging of psychopathy

Neuroimaging studies in psychopathy have reported heterogenous results covering all four lobes in the brain (De Brito et al., 2021a). A recent systematic review concluded that decreased GMV in fronto-temporal areas, amygdala, hippocampus, INS and CC are most consistent neuroanatomical correlates of psychopathy (Johanson et al., 2020). A recent VBM meta-analysis also found general reduced mean volume and total GMV in psychopathy (Tully et al., 2023a). Two latest meta-analyses suggest that GMV reduction in the OFC and dlPFC are the most consistent neural correlates of psychopathy (De Brito et al., 2021b; Yang and Raine, 2009). However, decreased GMV in amygdala, INS, ACC, frontal pole and nucleus lentiformis have also been observed in meta-analyses (Aoki et al., 2014; Tully et al., 2023a; Yang and Raine, 2009). Increase of GMV has been observed in only one of the meta-analysis and it was focused to fusiform gyrus, parietal lobule, cingulate gyrus and postcentral cortex (Aoki et al., 2014). Decreased GMV in the frontotemporal and limbic areas can be seen also in children with CD/CU, supporting their precursory role for psychopathy (De Brito et al., 2019; Raine, 2018; Rogers and De Brito, 2016). Moreover, the same brain areas where criminal psychopathy shows structural alterations are also associated with psychopathic traits in healthy volunteers (Nummenmaa et al., 2021). Finally, DTI studies have presented reduced white matter integrity of uncinated fasciculus in adults with psychopathy and antisocial behavior compared to healthy controls but also compared to individuals with antisocial behavior without psychopathy (Waller et al., 2017).

4.2. Functional imaging of psychopathy

FMRI meta-analyses of psychopathy have shown heterogenous findings across the brain, but the most persistent alterations in activation have been found in the PFC. At network level, the task-based fMRI meta-analyses have shown persistently lower activation of the affective salience network (Deming and Koenigs, 2020; Nelson Aguiar et al., 2023). Rs-fMRI studies have reported aberrant connectivity in the DMN, fronto-parietal network and in their interconnection associated with psychopathy traits (Cohn et al., 2015; Espinoza et al., 2019; Philippi et al., 2015; Pu et al., 2017; Umbach and Tottenham, 2021; Winters et al., 2021). In studies of connectivity, one task-based meta-analysis associated psychopathic traits with higher connectivity in the anterior INS/claustrum and lower connectivity in the cerebellum (Dugré and De Brito, 2025). A more detailed breakdown of the results of the task-based fMRI meta-analyses is presented below (**Table 5)**.

Meta-analyses across the tasks have shown divergent findings of hyperactivity and hypoactivity of the PFC, but with hypoactivation of the ACC being the most

consistent finding (Deming and Koenigs, 2020; Dugré and De Brito, 2025; Nelson Aguiar et al., 2023; Poeppl et al., 2019; Yang and Raine, 2009).

4.2.1. Social tasks

A meta-analyses by Dugre et al found that during social tasks (face processing, ToM and emotion processing) there is hyperactivation of putamen, precuneus, medial prefrontal cortex, dlPFC, cerebellum and rolandic operculum in psychopathy, whereas hypoactivation is found in the medial cingulate cortex (MCC), hippocampus, inferior and medial occipital cortex, IFG and fusiform gyrus (Dugré et al., 2020). The face perception meta-analyses in psychopathy have revealed decreased activation in amygdala, vmPFC, ACC, superior and IPL, middle temporal gyrus and fusiform gyrus, but increased activity in INS (Berluti et al., 2023; Penagos-Corzo et al., 2022). According to meta-analysis by Lenzen et al. 2021, ToM tasks show hyperactivation of INS and IPL in psychopaths versus controls, whereas hypoactivation is observed in the dorsomedial, inferior and lateral prefrontal cortex, amygdala and midbrain (Lenzen et al., 2021). There is only one brain imaging meta-analysis on the social reward in psychopathy, which found no differences in task-related brain activity (Dugré et al., 2020).

4.2.2. Non-social tasks

To my knowledge, there is only one meta-analysis by Dugre et al (2020) studying brain activity during non-social tasks in psychopathy. This study reported hypoactivation of the premotor cortex, aINS, middle temporal and middle frontal gyri and cerebellum during inhibitory tasks in psychopathy, while there was no consistent hyperactivation across individual studies (Dugré et al., 2020). In acute threat tasks, studies have found hypoactivation of the bilateral dorsal ACC, SMA, MCC, aINS, triangular part of the IFG, middle occipital gyrus, dlPFC, inferior parietal gyrus and inferior temporal gyrus (Dugré et al., 2020). This meta-analysis found no differences in brain activation between individuals with and without psychopathy during non-social reward tasks. Processing punishment of monetary loss was associated with hyperactivation of cerebellum and midbrain, whereas hypoactivation was found in the premotor cortex in passive avoidance and monetary incentive delay tasks.

Table 5. Overview of the task-based fMRI meta-analyses in Psychopathy. Areas with higher or lower fMRI activation in at least two meta-analyses are included in the table, excluding areas with contradictory findings (Berluti et al., 2023; Deming and Koenigs, 2020; Dugré et al., 2020, 2020; Dugré and De Brito, 2025; Herpers et al., 2014; Lenzen et al., 2021; Murray et al., 2018; Nelson Aguiar et al., 2023; Penagos-Corzo et al., 2022; Poeppl et al., 2019; Umbach and Tottenham, 2021; Yang and Raine, 2009).

Social tasks			Non-social tasks		
Social	Putamen Precun mPFC dlPFC Cereb OpR	↑	Inhibitory control	-	↑
	MCC Hippocampus IOG MOG IFG	↓		PreCG Insula MTG MFG Cereb	↓
Face processing	Insula	↑	Punishment processing	Cereb Tegmentum	↑
	IPL SPL ACC vmPFC Amygdala FG MTG	↓		PreCG	↓
Theory of mind	Insula IPL	↑	Acute threat response	-	↑
	dmPFC InfPFC Midbrain Amygdala IPL latPFC	↓		dACC SMA MCC Insula IFG MOG dlPFC IPG ITG	↓

4.3. Molecular imaging of psychopathy

Mainly due to their role in aggressive and impulsive behavior, dopamine and serotonin have been the most widely examined neurotransmitters in studies of psychopathy (Frazier et al., 2019; Glenn and Raine, 2008; Yildirim and Derksen, 2015a). Preliminary results have also suggested a possible role for endogenous opioid system in psychopathy (Bandelow and Wedekind, 2015).

Animal and human studies propose that psychopathy is related to increased tonic striatal dopaminergic activity, but dysfunctional dopaminergic functioning in PFC (Yildirim and Derksen, 2015a). In addition, antipsychotic dopamine antagonists have been shown to reduce aggressive behavior in humans across multiple diagnoses (Bak et al., 2019; van Schalkwyk et al., 2018). Functional

imaging studies in humans have presented also evidence for striatal hyperactivity in psychopathy, but there are currently only two PET-studies on dopamine system and psychopathy (Glenn and Yang, 2012). PET-imaging study using [18F]fallypride has presented lower baseline D2R availability and enhanced dopamine release in NAcc after amphetamine challenge to predictict psychopathic traits in a community sample (Buckholtz et al., 2010a), suggesting a hypersensitivity in the striatal dopaminergic reward system. Additionally, Lukkarinen et al. established also to show lower baseline D2R availability with [11C]raclopride in a violent offender group compared to controls (Lukkarinen et al., 2024).

Human and animal studies have suggested a dysfunction of the endogenous opioid rewarding system in psychopathy (Bandelow and Wedekind, 2015) and opiate addiction has been associated with antisocial behavior (Ross et al., 2005). Additionally, psychopathy has been associated with down-regulation of the mu-opioid receptor gene OPRD1 (Tiihonen et al., 2020). However, a PET-imaging study by Lukkarinen et al. found no significant group differences in MOR binding between the psychopathy and control group (Lukkarinen et al., 2024).

Serotonin has been suggested to play a further role in the development of psychopathy through its modulatory role in dopaminergic functioning (Glenn and Raine, 2008; Yildirim and Derksen, 2015a). In addition, serotonin plays a bidirectional role in emotional hyporesponsivity and emotional dysregulation, which are presented opposingly in primary and secondary psychopathy (Yildirim and Derksen, 2013). One PET-imaging study has found a strong positive correlation between the level of psychopathy and serotonin tracer binding in the nucleus caudatus and OFC in violent offenders (da Cunha-Bang et al., 2017). Another PET-study with intermittent explosive disorder patients presented a positive correlation between callous psychopathy traits and serotonin transporter (SERT) binding in ACC (van de Giessen et al., 2014).

5. Similarities and differences between ASD and psychopathy

ASD and psychopathy are two clinically distinct disorders, but they also share a lot of features (**Figure 4**). As these two conditions are both strongly heritable, have their origin in the early childhood, present structural and functional brain abnormalities and neurocognitive deficits with stabile developmental course resulting to impairments in adulthood, they can both be considered as neurodevelopmental disorders (De Brito et al., 2021a; Lord et al., 2022; Raine, 2018; Thapar et al., 2017). Moreover, ASD and psychopathy both have strong genetic background (McCrory, n.d.; Tick et al., 2016) and they may also share some of their genetic origin (Jones et al., 2009; O'Nions et al., 2015; Tick et al., 2016; Tiihonen et al., 2020).

The prevalence of comorbid ADHD, depression, alexithymia is higher in ASD and psychopathy as compared to neurotypical controls, whereas the risk of anxiety is related only to autism and secondary psychopathic traits (De Brito et al., 2021a; Hirota and King, 2023; Lockwood et al., 2013). The risk of aggressive behavior and difficulties in social relationships are elevated in both disorders (De Brito et al., 2019, 2021a; Fitzpatrick et al., 2016; Hill et al., 2014; Hirota and King, 2023; Kanne and Mazurek, 2011).

Psychopathy and ASD are both associated with difficulties in recognizing emotional expressions from faces (Blair et al., 2001; Clark et al., 2008; Harms et al., 2010; Hastings et al., 2008; Marsh and Blair, 2008; Uljarevic and Hamilton, 2013; Woodworth and Waschbusch, 2008). Lack of empathy is an important feature in both disorders, but its manifestation differs in these disorders (Blair, 2008; Fitzgerald, 2019; Jones et al., 2010; Lockwood et al., 2013). While psychopathy is associated with diminished affective empathy and intact cognitive empathy, ASD on the opposite is associated with diminished cognitive empathy and intact affective empathy in adults (Maguire et al., 2024). Studies have reported impaired automatic mimicry (motor empathy) with intact deliberate imitative capability in both of these disorders, but results have been partly mixed (Ayache et al., 2025; Bons et al., 2013; Book et al., 2015; Carnevali et al., 2024; Edwards, 2014; Eigsti, 2013, 2013; Harmsen, 2019; Helt et al., 2021; Khvatskaya and Lenzenweger, 2016; Künecke et al., 2018; Kyranides et al., 2024, 2023; Luckhurst et al., 2017; McIntosh et al., 2006; Meffert et al., 2013; Mier et al., 2014; Oberman et al., 2009; O'Nions et al., 2017; Wagner et al., 2020). Challenges in social interaction and ToM are central to ASD (Gao et al., 2023; Hirota and King, 2023), whereas psychopathy is characterized by manipulative and conning behavior while ToM is thought to be intact (Blair and White, 2013). However, a recent meta-analysis showed that psychopathic traits exhibit also some impairments in both affective and cognitive ToM (Song et al., 2023). Primary psychopathy was associated with more severe deficits of ToM (Song et al., 2023). Moral judgement has been considered to be poor in psychopathy and more or less intact in ASD (Blair, 2008). However recent meta-analyses have reported only slight deficits of moral reasoning and decision-making in psychopathy (Marshall et al., 2018) and systematic reviews have argued on weak moral reasoning but intact decision-making in ASD (Dempsey et al., 2020).

The prevalence of aggressive behavior in children and adolescents with ASD has been evaluated to be high (25-68%) and this is not associated with ID or the severity of ASD symptoms (Hill et al., 2014; Kanne and Mazurek, 2011). However, lower intelligence is a risk factor for aggressive behavior in general (De Brito et al., 2021a; Ttofi et al., 2016) and ASD has been shown to be a risk factor for aggressive behavior in people with ID (McClintock et al., 2003). Reactive aggression is thought to be more prevalent in ASD than proactive (Kirst et al., 2022; Oubrahim and Combalbert, 2021; Pouw et al., 2013) and self-injurious behavior is also common (Labarca et al., 2025). Reactive aggression in ASD is mainly associated with

impaired emotion regulation and overstimulating environment (Pouw et al., 2013). Unlike in neurotypical individuals, in children with ASD affective empathy is positively and cognitive empathy is negatively correlated with reactive aggression (Pouw et al., 2013). Finally, ASD is associated with deficits in inhibitory control that are independent of comorbid ADHD and are modulated by age and intellectual functioning (Tonizzi et al., 2022).

Psychopathy is related to both reactive and proactive aggression (De Brito et al., 2021a; Jambroes et al., 2018). The traits of secondary psychopathy (impulsive and irresponsible) with low verbal intelligence are correlated with reactive aggression, whereas primary psychopathy traits (callous unemotional) correlate with violence in general and are not moderated by intelligence (Jambroes et al., 2018). Additionally, in people with ID and ASD, primary psychopathy traits are associated with more severe aggression and self-injurious behavior and stereotypical behavior (Álvarez-Couto et al., n.d.).

Autistic and psychopathic traits overlap in the general population (Barnard-Brak and Richman, 2021; Loureiro et al., 2018). Despite the fact that ASD might be underdiagnosed in forensic settings (Loureiro et al., 2018), both disorders are over-represented in high security forensic facilities (Fazio et al., 2012; Im, 2016; Jeandarme et al., 2022; Murphy, 2020; Reiss et al., 1999). The prevalence of diagnostic psychopathy in prison is estimated to be 16-25 %, but prevalence rates for ASD vary greatly from 0.2 to 62.8 % and the estimates are likely to be unreliable due to methodological reasons (Collins et al., 2023; De Brito et al., 2021a; King and Murphy, 2014). However, both psychopathy and ASD traits are suggested to be over-presented in prison (Loureiro et al., 2018). Despite these aforementioned connections, only psychopathy has been related to violence and criminal behavior (Del Pozzo et al., 2018; Im, 2016; King and Murphy, 2014; Murrie et al., 2004). Furthermore, individuals with ASD are rather law abiding and prone to be victims of violence and crime themselves (Allely et al., 2017; Im, 2016; Trundle et al., 2023).

Psychopathy and ASD are regarded as distinct disorders and their co-occurrence is considered as a double diagnosis, which is often referred as criminal autistic psychopathy in the literature (Carthy and Murphy, 2021; Fitzgerald, 2019; Maguire et al., 2024; Murphy et al., 2024; Rogers et al., 2006). Based on self-report questionnaire studies, the prevalence of callous unemotional traits and psychopathy in people with ASD or high autistic traits has been evaluated to range from 25 % to 56 % (Maguire et al., 2024). There are only few studies on comorbidity between these two disorders in forensic settings, which show no correlation between psychopathy and ASD traits (Maguire et al., 2024; Murphy et al., 2024). Only two studies have used PCL-R to evaluate psychopathy in forensic psychiatric autistic patients and they found no diagnostic comorbidities, but a positive correlation with affective components of psychopathy and autistic traits (Murphy et al., 2024).

Problems in higher-order cognition are also common in both ASD and psychopathy. At least 30% of children with ASD do not acquire spoken language and the global prevalence of ID in ASD is evaluated to be up to 33% (Braconnier and Siper, 2021; Elsabbagh et al., 2012). A term "highly functioning autism" has been referred to ASD individuals without ID (Intelligence Quotient IQ ≥ 70) (Alvares et al., 2020). However, low adaptive functioning is common in ASD even without ID and IQ is regarded as a poor predictor of functional abilities in ASD without ID (Alvares et al., 2020; Braconnier and Siper, 2021). Savant skills, that exceed conventional human abilities, for example, in arithmetic, arts or memorizing, are present in approximately 29% of ASD individuals (Hirota and King, 2023).

Secondary psychopathy is associated with criminality and lower IQ, whereas primary psychopathy has been related to better adaptive functioning and success in life, but its associations to IQ have been discordant (Durand et al., 2023; Isen et al., 2018; Michels, 2021; Sánchez De Ribera et al., 2019; Wallace et al., 2022). There is a lack of awareness and established diagnostics of personality disorders in people with ID and no reliable evidence of increased prevalence of psychopathy in ID have been presented in the present scientific literature (Morrissey and Hollin, 2011). Recent meta-analyses have shown that deficits of executive functions in psychopathy are rather small, related to antisocial traits and centralized to inhibition and planning problems, whereas ASD is related to moderate and broad spectrum of problems in executive functions, cognitive flexibility in particular (Braconnier and Siper, 2021; Burghart et al., 2024; Demetriou et al., 2018).

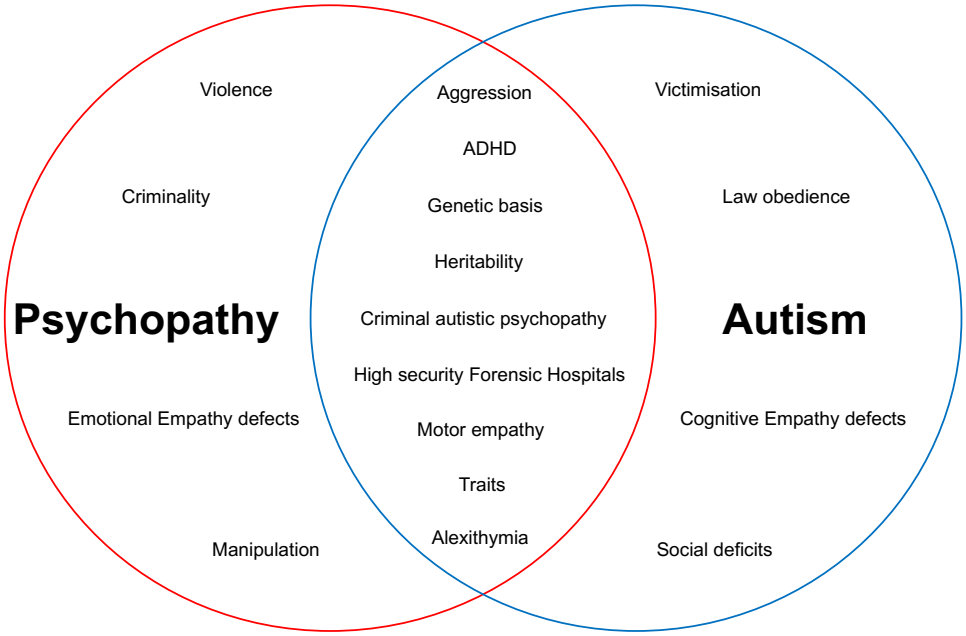


Figure 4. Shared features and contrasts between ASD and psychopathy. The data is collected from Rogerts et al (2006), Carthy et al (2021), Im et al (2016), Allely et al (2016), Murphy et al (2020), Loureiro et al (2018), Barnard-Brak and Richmann (2019), Lockwood et al (2013), Fitzpatrick et al (2016), Kanne and Mazurek (2011), Raine (2018), Viding and McCrory (2012), Tick et al (2015), Ó Nions et al (2015), Tick et al (2016), Tiihonen et al (2020), Murrie et al (2014), Im (2016), King and Murphy (2014), Fitzgerald (2018).

5.1. Structural imaging of ASD and psychopathy

Whereas psychopathy is linked with decreased frontotemporal GMV from childhood CD/CU to adulthood (De Brito et al., 2019; Johanson et al., 2020; Raine, 2018; Rogers and De Brito, 2016), ASD is related to more complex aberrant growth trajectory leading to increased frontal but decreased temporal GMV in adulthood (Boedhoe et al., 2020; Eric Courchesne et al., 2011; Van Rooij et al., 2018). There is only one previous structural study comparing these disorders directly at the level of social and antisocial traits (Boedhoe et al., 2020; Johanson et al., 2020; Van Rooij et al., 2018; Wallace et al., 2012). In a study of 323 typically developing and normally functioning adolescents, elevated psychopathic traits were associated with lower cortical thickness in the anterior PFC and elevated ASD traits were associated with lower cortical thickness in STS and TPJ. The only overlapping region of cortical thinning as a function of psychopathic and autistic traits was in the left medial parietal cortex (Wallace et al., 2012).

5.2. Functional imaging of ASD and psychopathy

Functional imaging meta-analyses have shown aberrancies of frontal lobe, cingulate cortex and amygdala in both ASD and psychopathy during social tasks (Di Martino et al., 2009; Dickstein et al., 2013; Dugré et al., 2020; Herpers et al., 2014; Patriquin et al., 2016). During face processing tasks both disorders have been linked with aberrancies of ACC, STS, and fusiform gyrus (Berluti et al., 2023; Di Martino et al., 2009; Patriquin et al., 2016; Penagos-Corzo et al., 2022; Philip et al., 2012; Sugranyes et al., 2011), whereas during ToM tasks aberrant function has been found in the IPL and PFC (Lenzen et al., 2021; Philip et al., 2012; Sugranyes et al., 2011). Alterations of DMN have also been associated with both disorders (Carlisi et al., 2017; Deming and Koenigs, 2020; Di Martino et al., 2009; Dugré and Potvin, 2021; Ilioska et al., 2023; Lau et al., 2020, 2019; Liloia et al., 2024; Umbach and Tottenham, 2021; Wang et al., 2021; W. Wang et al., 2018).

There are only two previous fMRI studies comparing these two disorders directly. One fMRI study using empathy tasks found reduced responses in cognitive empathy associated vmPFC with in youths with ASD during emotional recognition task compared to neurotypical controls (Klapwijk et al., 2016). In turn, youths with CD/CU traits showed reduced responses in emotional empathy related brain regions (IFG, aINS) during emotional resonance compared to controls (Klapwijk et al., 2016). During the emotional resonance task both study groups showed reduced response in emotional processing area, the amygdala, while youths with ASD showed reduced responses also in the hippocampus compared to neurotypicals (Klapwijk et al., 2016). In another fMRI study using ToM tasks, the children with ASD showed atypical neural processing in the medial prefrontal cortex compared to typically developing children, but there was no difference between children with conduct problems and high callous unemotional traits and typically developing children (O'Nions et al., 2014). In the ASD group, fMRI responses in the medial prefrontal cortex and TPJ correlated with symptom severity measured with ADOS (O'Nions et al., 2014).

5.3. Molecular imaging of ASD and psychopathy

PET-imaging research of ASD and psychopathy has focused mainly on serotonin and dopamine neurotransmitter systems (Buckholtz et al., 2010a; da Cunha-Bang et al., 2017; Lukkarinen et al., 2024; Tan et al., 2022; van de Giessen et al., 2014; Zürcher et al., 2015). Currently there are no PET-imaging studies comparing these disorders directly.

C. Objectives

This PhD thesis aimed to explore similarities and differences of the social brain in psychopathy and autism spectrum disorder (ASD) using structural and functional brain imaging methods (MRI, fMRI, and PET). Study I focused on investigating the structural brain alterations in psychopathy and ASD. Study II mapped functional brain responses in these two conditions during social perception tasks. Study III investigated atypical neuromolecular functioning associated with ASD at the level on dopamine and endogenous opioid neurotransmission.

D. Materials and methods

1. Subjects

We recruited altogether 65 volunteers for the studies. All participants gave informed, written consent and were compensated for their participation. The study protocol was approved by the ethics board of the Hospital District of Southwest Finland (ETMK Dnro: 60/1801/2017 §181, §588), and the study was conducted in accordance with the Declaration of Helsinki. The study also obtained a research permit from the Hospital District of Helsinki and Uusimaa since the ASD group participants were largely recruited from this area (HUS/161/2019 §22, HUS/153/2021 §1).

For minimizing confounding factors and maximizing statistical power, the study was run using a male-only sample with a restricted age range (20–50 years). In addition, a significant male overrepresentation is observed in both imprisonment rates and the prevalence of autism spectrum disorder (ASD) (Cúnico and Lermen, 2020; Hirota and King, 2023). The general exclusion criteria were current use of narcotics, current abusive use of alcohol (over 14 U /week), previous or current severe axis I psychiatric illnesses assessed by SCID-I interview (Spitzer et al., 1992), autoimmune illnesses, current medical conditions, exceptional risk of violence and the standard MRI exclusion criteria. Structural brain abnormalities that were clinically relevant or could bias the analyses were excluded by a consultant neuroradiologist.

For the self-report evaluation of psychopathy and ASD, the participants completed the Levenson Self-Report Psychopathy Scale (LSRP) questionnaire (Levenson et al., 1995) and Autism-Spectrum Quotient (AQ) questionnaire (Baron-Cohen et al., 2001; Bishop et al., 2004). AQ comprises 50 questions measuring five different facets of autism spectrum disorder: social skill, attention switching, attention to detail, communication, and imagination. The cut-off limit in AQ for clinically significant ASD traits is total score of 32 (Baron-Cohen et al., 2001). LSRP measures the primary and secondary dimensions of psychopathy with 26 questions. The cut-off limit for psychopathy in LSRP is defined as total score of 48 or below

for non-psychopathic and 58 or more for psychopathic respondent, whereas total score of 49 to 57 is considered as mixed respondents (Brinkley et al., 2001).

The education of all the participants was classified in three different categories: (1) primary school, (2) secondary degree, (3) university degree (**Table A2**). All the participants were screened for their clinical status, with comprehensive general blood laboratory exams, including a urinary test for the use of narcotics.

1.1. ASD group

The ASD group consisted of twenty-two male participants with ASD diagnosis (mean age 28 years, range 20–40 years), recruited from the Helsinki and Turku University Hospital Neuropsychiatric Clinics, with one subject also recruited from Neuropsychiatric Clinic Proneuron, in Espoo (https://proneuron.fi/). The only inclusion criterion was a valid autism spectrum disorder diagnosis (DSM-5 299.00). The diagnoses were verified by a neuropsychologist, neurologist, and psychiatrist following DSM-5 criteria based on patient history, all accessible information from birth records, well-baby clinics, and school healthcare. Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) assessment (Esler et al., 2015) was also performed by trained, research-reliable clinical psychologist to quantify the autism severity in this group.

Six of the ASD participants had additional diagnosis of ADHD and eight had additional diagnosis of mood or anxiety disorders. As all the participants in the ASD groups scored below 49 in the LSRP, they were considered non-psychopathic and PCL-R evaluation was not deemed necessary (Brinkley et al., 2001). There was no history of excessive alcohol use or substance use in the ASD group. Twenty individuals from the ASD group took part in Study I (MRI) and Study II (fMRI). Possible opioid and dopaminergic medications were withdrawn before MRI and fMRI measurements, but it was not possible to execute a total discontinuation of the medications. Clinical information of these ASD subjects is found in **Table 6-7**. After two additionally recruited participants, altogether sixteen individuals from the ASD group took part in Study III (PET). These ASD group participants did not have any opioid or dopaminergic medication and the clinical information and characteristics of these ASD participants is found in **Table 6-7**.

1.2. Violent offender group

The violent offender group consisted of 19 male inmates with high psychopathy traits (mean age 31 years, range 23–45 years) from Turku Prison who had been sentenced for murder (n = 5), manslaughter (n = 5), attempted manslaughter (n = 3), or grievous bodily harm (n = 6). The inclusion criterion for the group was a current sentence for at least one violent crime (murder, manslaughter, rape, assault). Psychiatric diagnoses of the offender group were based on prison health care and forensic psychiatric violence risk assessments, or thorough forensic

psychiatric examination reports concerning legal responsibility, two recruitment interviews, and semi-structured PCL-R interviews. Psychopathy of the offenders was evaluated with semi-structured interview by experienced forensic psychiatrists or psychologists based on the PCL-R (Hare, 2011). Two of the offenders refused to be evaluated with this interview. Final consensus diagnoses were made by two medical specialists both in psychiatry and forensic psychiatry with 13–25 years of experience in the field of prison psychiatry, who were assisted by a psychologist with a 15- year working history in a Psychiatric Hospital for Prisoners.

Altogether 16 participants had antisocial personality disorders, as defined by DSM-5 criteria (American Psychiatric Association, 2022), and 3 who fulfilled the other criteria of antisocial personality disorder, except the criterion of conduct disorder before the age of 15 years. History of excessive alcohol use was present in 13 participants, and 18 participants had self-reported or documented use of illegal substances (black market benzodiazepines, pregabalin or opioids, cannabis, amphetamines, gamma-hydroxybutyrate, methylenedioxypyrovalerone, anabolic steroids, and cocaine). Information concerning the severity of abuse was considered unreliable. One participant in the offender group scored 35 in AQ but showed no evidence of comorbid ASD in clinical evaluations. ADOS-2 evaluations in this group were not considered necessary. However, three of the offender group did not complete the AQ questionnaire. Clinical information of offenders is found in **Table 6-7**.

All the offenders took part in the study I (MRI) and study II (fMRI). The possible opioid and dopaminergic medications were mostly withdrawn before the measurements, but all medication could not be fully discontinued. The offenders were each escorted by two prison guards to the local research institute for the brain imaging study. Clinical information of offenders is found in **Table 6-7**.

1.3. Control group

The control group consisted of 24 male participants with clean criminal record and no history of neurological or psychiatric disorders (mean age 29 years, range 20–49 years). They were screened for medical conditions from their patient histories, and their use of prescribed medication was double-checked from the Finnish medical database. All the participants in control group scored below the cut-off limits of 32 in the AQ and 49 in the LSRP and were considered non-autistic and non-psychopathic. Therefore, ADOS and PCL-R evaluations were not considered necessary for this group (Baron-Cohen et al., 2001; Brinkley et al., 2001). Nineteen control participants took part in Studies I (MRI) and II (fMRI), and after five additionally recruited participants, Study III (PET) included all the 24 control participants. Clinical information of the control participants is found in **Table 6-7**.

Table 6. Subject characteristics. *Statistically significant group differences ($p<0.05$). 1 Significant $p<0.05$ differences between groups except between ASD and Healthy controls in ONE-WAY ANOVA analyses.

	Study I-II			Study III	
	Controls[I-II]	**ASD[I-II]**	**Offenders[I-II]**	**Controls[III]**	**ASD[III]**
	Mean (Std.)	Mean (Std.)	Mean (Std.)	Mean (Std.)	Mean (Std.)
Age	29 (8)	28 (6)	31 (7)	29 (9)	30 (5)
n (males)	19	20	19	24	16
Education*					
No graduation	0	0	2	-	-
Primary School	0	3	11	-	2
Second degree	10	14	5	14	12
University	9	3	0	10	2
Psychopathy					
PCL-R	-	-	26 (5) *n*=17	-	-
LSRP primary [1]	22 (3)	23 (4)	31 (6) *n*=15	-	-
LSRP secondary*	13 (3)	17 (3)	20 (3) *n*=15	-	-
Autism					
AQ*	11 (4)	28 (6)	20 (6) *n*=16	12 (5)	28 (6)
ADOS-2	-	11 (4)	-	-	11 (5)
Handedness					
Right	16	13	16	20	9
Left	3	7	3	4	5
BMI	-	-	-	25 (2)	26 (7)

Table 7. Subject characteristics. [2]Medication stopped 1 day before the scanning.

	Study I-II			Study III	
	Controls[I-II]	**ASD[I-II]**	**Offenders[I-II]**	**Controls[III]**	**ASD[III]**
	Number of participants	Number of participants	Number of participants	Number of participants	Number of participants
Current diagnoses:					
Autism Spectrum disorder	-	20	-	-	16
Antisocial personality disorder	-	-	16	-	-
Borderline personality disorder	-	-	4	-	-
ADHD	-	6	5	-	2
Previous diagnoses:					
Mood and Anxiety disorder	-	8	4	-	6
Substance abuse	-	-	18	-	-
Alcohol abuse	-	-	13	-	-
Medication:					
SSRIs, SNRIs	-	4	5	-	3
Tricyclic antidepressants	-	-	4	-	-
Other antidepressants	-	1	-	-	-
Hypnotics and Anxiolytics	-	3	6	-	1[2]
Neuroleptics	-	-	6	-	-
Stimulants	-	2	1	-	-
Betablockers	-	-	2	-	-
Antihistamines	-	1	9	-	-
Levothyroxine	-	1	1	-	-
Melatonine	-	2	6	-	1

2. Overall study design

In study I we investigated the GMV in all the study groups using structural MRI imaging and VBM. In study two the participants completed facial and vocal expression perception tasks during fMRI. Study III involved PET-imaging of ASD and control group with two different radiotracers, [11C]raclopride binding to type II dopamine receptor (D2R) and [11C]carfentanil, binding to for mu-opioid receptors (MOR). **(Figure 5).**

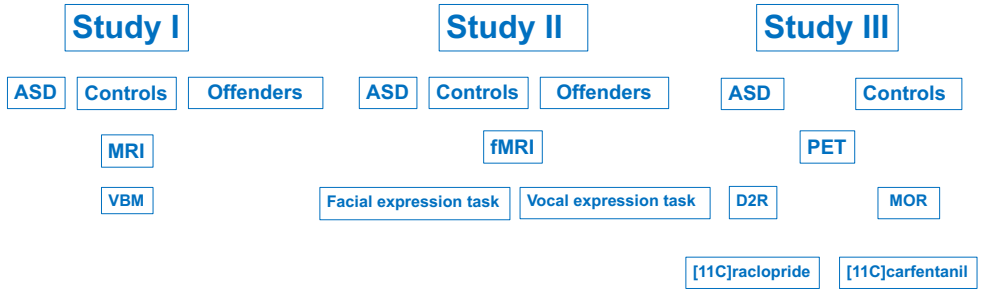


Figure 5. Overall study design in Studies I-III.

3. Methods

3.1. Study I

Structural MRI data were acquired from the participants in all three study groups with Phillips Ingenuity TF PET/MR 3 T scanner using T1-weighted sequence (TR 9.8 ms, TE 4.6 ms, flip angle 7°, 250 mm FOV, 256 × 256 voxel matrix) and isotropic voxel size (1 mm^3). SPM12 software was used for automated spatial normalization, tissue classification, and radio-frequency bias correction combined with the segmentation step to conduct the VBM. To account for differences in total brain size across subjects and volume changes caused by spatial normalization, we used non-linear transformation step as implemented in CAT12 toolbox. All the segmented, normalized, and modulated GM and WM images were finally smoothed using a Gaussian kernel of 8 mm full width at half maximum (FWHM).

3.1.1. Statistical analysis

Normalized and smoothed VBM images were analyzed with SPM12 using ANOVA F-tests and T-tests of the general linear models (GLM). We also evaluated GMV in frontal, temporal, INS and amygdala a priori regions of interest (ROI), defined by the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). In addition to the group comparisons, we conducted continuous analyses based on the LSRP and AQ questionnaire scores.

3.2. Study II

Functional T2∗-weighted echo-planar imaging sequence data (TR = 2600 ms, TE = 30 ms, 75° f lip angle, 240 mm FOV, 80 × 80 reconstruction matrix, 62.5 kHz bandwidth, 3.0 mm slice thickness, 45 interleaved slices acquired in ascending order without gaps) were acquired from a total of 206 (facial expression task) or 290 (laughter task) functional volumes with Phillips Ingenuity TF PET/MR 3 T

scanner. Anatomical T1 reference images from study I were processed for Study II using fMRIPrep 1.3.0.2 in a following manner: correction for intensity non-uniformity, skull-stripping, brain surface reconstruction, spatial normalization to the ICBM 152 nonlinear asymmetrical template version 2009c. Co-registration of functional images to the anatomical reference images, slice-time correction, spatial smoothing and automatic removal of motion artifacts was executed using ICA-AROMA software (Pruim et al., 2015) and images were resampled to the MNI152NLin2009cAsym standard space.

In the emotional facial expression task (**Figure 6**), participants viewed short video clips (5 s) of dynamic facial expressions of joy, disgust, and anger selected from Amsterdam dynamic facial expression set (ADFES) database (van der Schalk et al., 2011). All clips begun with a neutral face, which was followed by a dynamic display of the facial expression. Prior to each clip, participants were shown the first frame of the video (i.e. neutral face) for 3.5 s to avoid peaks in low-level visual activation due to simultaneous visual stimulus and motion onset. This was followed by the dynamic expression from neutral to full expression, with the full-blown phase held until the end of the clip. Each stimulus was followed by a random 4–8 s of rest period. Again, to avoid peaks in low-level visual cortical activations, a scrambled picture of the upcoming model was shown during the rest period. To keep participants focused on the task, 4 trials (out of 36 trials in total) contained a still picture of the neutral face instead of the video clip. Participants were asked to press the response button as soon as they detected a trial without any facial motion. These trials were excluded from the analysis. Previous work shows that these dynamic stimuli elicit consistent and expression-specific neural responses in emotion and face perception circuits (Volynets et al., 2020).

In the vocal expression task (**Figure 6**), the participants listened to short laughter and crying vocalizations and control stimuli which were generated by time-domain scrambling of the original sounds. The original stimuli have been previously validated and described in detail (O'Nions et al., 2017). The experiment was run using a blocked design. In each 16.5-s block, 5 2.5-s stimuli from 1 category (i.e. laughter, crying sounds, scrambled laughter, or scrambled crying sounds) were played with a 1-s silent period between stimuli. Order of the blocks were randomized. The blocks were interspersed with rest blocks lasting for 4–7 s. To keep participants focused on the task, an animal sound (vocalization of an alpaca) was presented randomly during 50% of the rest blocks. The participants were instructed to press the response button whenever they heard the alpaca, and the behavioral outcomes were inspected for the focus of attention. A total of 32 blocks (8 blocks per stimulus type) were run.

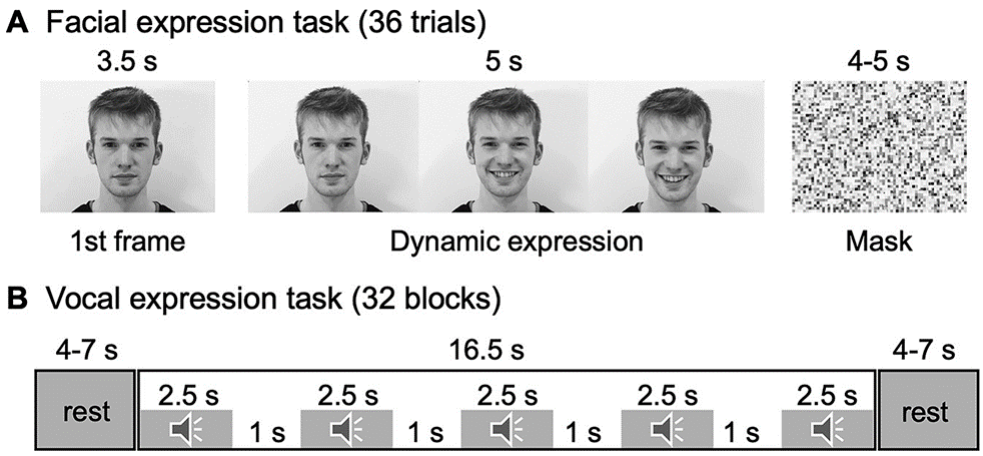


Figure 6. Experimental design for the facial expression task (A) and vocal expression task (B). Color images and videos were used in the facial expression task.

3.2.1. Statistical analysis

The fMRI data were analyzed in SPM12 using GLM (Wellcome Trust Center for Imaging, London, UK, (http://www.fil.ion.ucl.ac.uk/spm). For each participant, GLM was used to predict the regional effects of task parameters on BOLD indices of activation. The contrasts for facial expression task were happy, angry, or disgusted facial expressions versus static neutral faces. The contrasts for vocal expression task were laughter or crying sound versus corresponding scrambled sounds. Subject-wise contrast images were subjected to a second level (random effects) model for between-group comparisons for each effect of interest. We also fitted multiple regression model for the primary LSRP scores and AQ scores as a control analysis, whereas AQ correlated secondary LSRP these scores were left out from the analysis. In a complementary methodological approach, regions of interest (ROI) were defined in key regions involved in socioemotional processing: anterior, middle, and posterior cingulate cortices (ACC, MCC, PCC), precuneus, amygdala, caudate, putamen, and INS defined by the AAL atlas (Tzourio-Mazoyer et al., 2002). Additional ROIs were defined in somatomotor regions including primary motor cortex (M1), the secondary motor cortex (M2), the primary somatosensory cortex (S1), the secondary somatosensory cortex (S2). A region of interest (ROI) analysis using 2-sample t-test in R statistical software (version 3.6.3) was then performed for each ROI.

3.3. Study III

PET imaging was carried out with General Electric (GE) Healthcare Discovery VCT (ASD n = 2, Controls n = 17) and Discovery 690 PET/CT (ASD n = 14, Controls n = 7) scanners (spatial resolution ~ 5 mm FWHM). We measured the mean availability

of MOR with high-affinity agonist radioligand [11C]carfentanil [60] and D2R with agonist radioligand [11C]raclopride. The radioactivity in the brain was measured for 51 min after bolus injection. Scans with both radioligands were completed >2.5 h apart from each other on the same day to allow for radiotracer decay. The anatomical T1 images from study I were used for reference and normalization purposes. High-resolution anatomical T1-weighted images (TR 9.8 ms, TE 4.6 ms, flip angle 7^0, 250 mm FOV, 256 × 256 voxel matrix with 1 mm3 isotropic voxel size) from study I and seven additional scans were obtained with 3T PET-MRI scanner (Philips Ingenuity TF PET-MR device, Philips Healthcare) for reference and normalization purposes.

PET images were preprocessed in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) using in-house Magia pipeline (Karjalainen et al., 2020) (https://github.com/tkkarjal/magia), which utilizes SPM12 (The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, https://www.fil.ion.ucl.ac.uk/spm/software/spm12) in the PET data motion correction and image registration and FreeSurfer (version 6.3, https://freesurfer.net) in an automated ROI delineation. Parametric BP_{ND} images were calculated for voxel-level analysis with basis function implementation of SRTM (bfSRTM) with 300 basis functions. Before the parametric image calculation, the dynamic PET images were smoothed using a Gaussian kernel with 4 mm full width at half maximum to reduce the effect of noise in voxel-level bfSRTM fit. The resulting parametric images were further normalized into MNI152 space and smoothed again using a Gaussian 4 mm filter.

We used altogether 12 MOR binding ROIs involved in reward, motivation and socioemotional processing extracted from MRI by using FreeSurfer (striatal: caudate, globus pallidus, NAcc, and putamen, extrastriatal: amygdala, thalamus, dorsal ACC, rostral ACC, OFC, posterior cingulate cortex (PCC), INS and hippocampus) (Chevallier et al., 2012; Fields and Margolis, 2015; Fuccillo, 2016; Hirvonen et al., 2009; Majuri et al., 2018; Manninen et al., 2017; Nummenmaa et al., 2015; Pellissier et al., 2018; Reeves et al., 2022; Smith et al., 2009; Turtonen et al., 2021; Weinstein, 2023). Since [11C]raclopride binds reliably only in the striatum (Svensson et al., 2019), we restricted the [11C]raclopride analysis to striatal ROIs (Hirvonen et al., 2003; Malén et al., 2022; Seeman et al., 2006; Zürcher et al., 2021), with the exception of including thalamus and amygdala because of their striatal connections and relevance in ASD (Atzil et al., 2017; Baron-Cohen et al., 2000; Chevallier et al., 2012; Fuccillo, 2016; Hirvonen et al., 2003; Kohls et al., 2012; Malén et al., 2024; Murayama et al., 2022; Sato et al., 2023; Schuetze et al., 2016). Reference tissues volumes (cerebellum for [11C]raclopride and occipital cortex for [11C]carfentanil) were automatically adjusted to account for specific radioligand binding, as described previously (Karjalainen et al., 2020). Specific regional binding of [11C]raclopride and [11C]carfentanil was quantified as BP_{ND} using the SRTM (Lammertsma and Hume, 1996).

3.3.1. Statistical analysis

Full-volume analysis (A) of the normalized and smoothed [11C]raclopride and [11C]carfentanil images was carried out with SPM12 using a two-sample Student's t-test, while controlling for scanner type. The results were corrected for multiple comparisons in cluster level using false discovery rate (FDR) with significance level of $p<0.05$. [11C]carfentanil analysis included the whole brain volume, whereas voxel-wise [11C]raclopride analysis was restricted to striatum, as BP_{ND} for this ligand can be reliably estimated only within this subregion (Svensson et al., 2019).

Statistical analysis for the ROI data (B) was performed using R software (version 3.5.1, The R foundation, Vienna, Austria) and linear mixed-effects models (LMMs), by including a random intercept to control for the potential differences between PET scanners. Before the LMM analysis, all BP_{ND} values were log-transformed to ensure normality. Normality of the model residuals was evaluated with the Shapiro-Wilk test and checked visually with density and Q-Q plots. Homogeneity of variance was verified separately for both scanners with Levene´s test. The results were corrected for multiple comparisons using Holm's method.

1. We first tested for overall significant differences between the groups by including group as a fixed factor and participant, ROI and scanner type as random effects, allowing their intercepts to vary freely.
2. As our primary interest with D2R availability was the striatum, the striatal ROIs were analyzed first separately and then together with the thalamus and amygdala ROIs (Svensson et al., 2019).
3. We then set up post-hoc analysis for assessing group differences in each ROI separately, by specifying group as a fixed factor and scanner type as a random effect in LMM.
4. The association between AQ scores and regional radioligand availability were analyzed with LMM, with AQ and age as a fixed factor and scanner type as a random effect.
5. Associations between regional [11C]carfentanil and [11C] raclopride BP_{ND} were estimated using Pearson correlations. Group differences in the regional associations in D2R/MOR availability were tested using Fisher's z-test. A standard neuroimaging tool for matrix correlations, Mantel's test (Baldassarre et al., 2021; Glerean et al., 2016; Kheiri et al., 2013) was used to examine the similarity of the regional correlation structures of D2R/MOR availability between the groups.

3.3.2. Meta-analysis

To summarize the current data on striatal dopamine PET-imaging studies in ASD we conducted a meta-analysis (C). A PubMed search was conducted on Oct. 3rd, 2023, using the keywords "autism spectrum disorder", "PET", "positron emission tomography" and "dopamine". Moreover, a complementary search with Google Scholar was conducted to confirm that no studies were missing. Finally, we screened three of the latest review articles on the issue to ensure the full coverage

of our research (Kowalewska et al., 2022; Li et al., 2021; Tan et al., 2022). Altogether, we found nine potentially eligible articles (Ernst et al., 1997; Fernell et al., 1997; Kubota et al., 2020; Murayama et al., 2022; Nakamura et al., 2010; Nieminen-von Wendt et al., 2004; Schalbroeck et al., 2021b, 2021a; Zürcher et al., 2021), but only six reported data on striatal ROIs. Two of these six articles used the same data, so only one of them was included. Together with our results presented here a total number of six articles were included in the meta-analysis. All the articles were evaluated by three independent researchers of our group for inclusion in the meta-analysis. There was only one previous study using [11C]raclopride tracer (Zürcher et al., 2021) measuring D2R availability, whereas the other studies used [18 F]FDOPA (Ernst et al., 1997; Nieminen-von Wendt et al., 2004; Schalbroeck et al., 2021b, 2021a) measuring presynaptic dopamine synthesis capacity or D1R binding [11 C]SCH23390 (Kubota et al., 2020) as tracers. As one of the articles presented the required data only in their supplemental figure and it was also not readily accessible from the authors, we used plot-digitizer tool to extract baseline values from the accessible figure (Zürcher et al., 2021). Based on reported striatal group means, standard deviations and sample sizes, we calculated the standardized mean difference (SMD, Cohen´s d) for each study and a pooled sample size weighted SMD with R software metafor package using the fixed and random effects approach.

E. Summaries of the original studies

1. Study I: Brain structural alterations in autism and criminal psychopathy

The human social brain comprises of large-scale networks spanning all major brain lobes (Fernández et al., 2018; Henry et al., 2016). Psychopathy and autism spectrum disorder are both considered as developmental neuropsychiatric disorders of social cognition (De Brito et al., 2021a; Lord et al., 2022; Raine, 2018; Thapar et al., 2017). Despite the differences in the clinical profiles, both disorders are overpresented in high security forensic hospitals and share some of their clinical characteristics, comorbidities and genetic basis (Allely et al., 2017; De Brito et al., 2021a; Hirota and King, 2023; Im, 2016; Jeandarme et al., 2022; King and Murphy, 2014; Maguire et al., 2024; Murphy, 2020; Murphy et al., 2024; Reiss et al., 1999; Tiihonen et al., 2020).

In Study I we used structural MRI to compare brains of 19 control, 20 ASD and 19 violent offender participants with high psychopatic traits. We utilized VBM to compare the regional GMV between participants belonging to either of these study groups as well as a group of controls.

1.1. Results

The pair-wise comparison revealed lower GMV in right temporal pole and left IFG of offender versus ASD group (**Figure 7**). In comparison with controls, both offender and ASD groups had lower GMV in the precentral cortex (**Figure 8**). Additionally, the ASD group had lower GMV in left precuneus, right culmen of vermis, and the right cerebellum areas compared to controls (**Figure 7**). The offender group in turn had lower GMV in the bilateral INS, left frontal pole, cingulate gyrus, left inferior temporal gyrus, and left fusiform cortex compared to controls (**Figure 7**). ROI-analyses revealed lower GMV of frontotemporal areas in psychopathy group compared to controls and ASD, but also confirmed the overlapping finding in the precentral cortex of both disorders compared to controls. ASD group did not present any significant differences in ROI-analyses compared to controls.

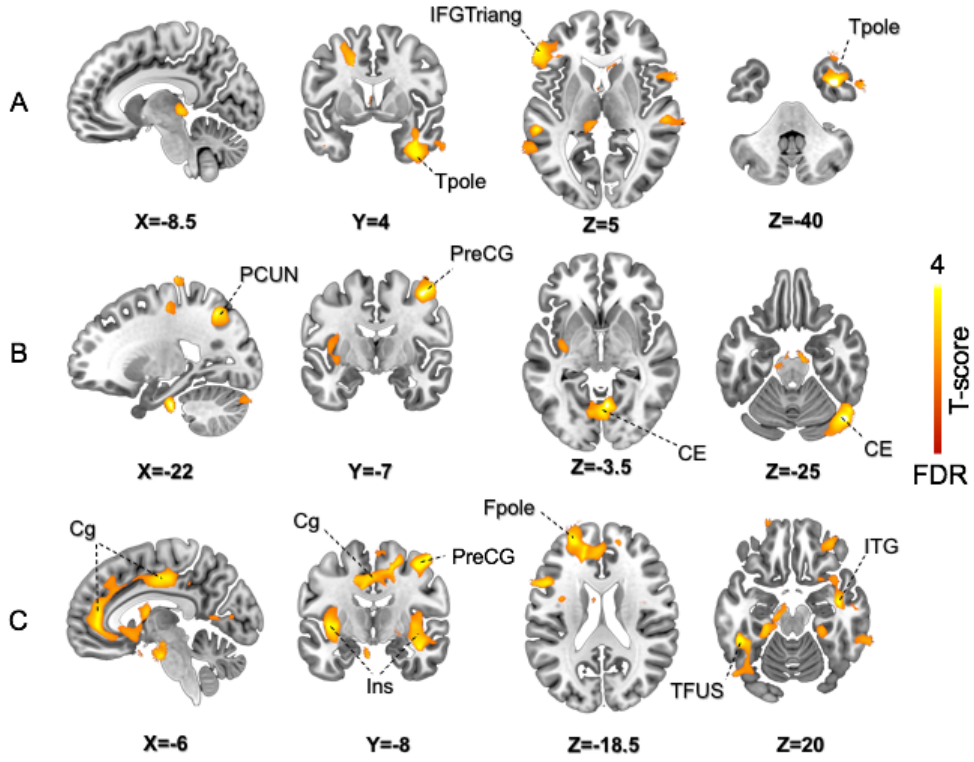


Figure 7. A. Brain regions with lower GMV in Offender versus ASD group. The data is FDR-thresholded at p < 0.01. Tpole = Temporal pole, IFGtriang = Inferior Frontal Gyrus, Triangular part B. Brain regions with lower GMV in ASD versus Controls. The data is FDR-thresholded at p < 0.01 PreCG = Precentral Gyrus, PCUN = Precuneus, CE = Cerebellum C. Brain regions with lower GMV in Offenders vs Controls. The data is FDR-thresholded at p < 0.01 PreCG = Precentral Gyrus, Fpole = Frontal pole, INS = Insula, Cg = Cingulate Gyrus, ITG = Inferior Temporal Gyrus, TFUS = Temporal Fusiform Gyrus. The range from FDR correction to T-value of 4 is used for better visualization of the variance in the scale.

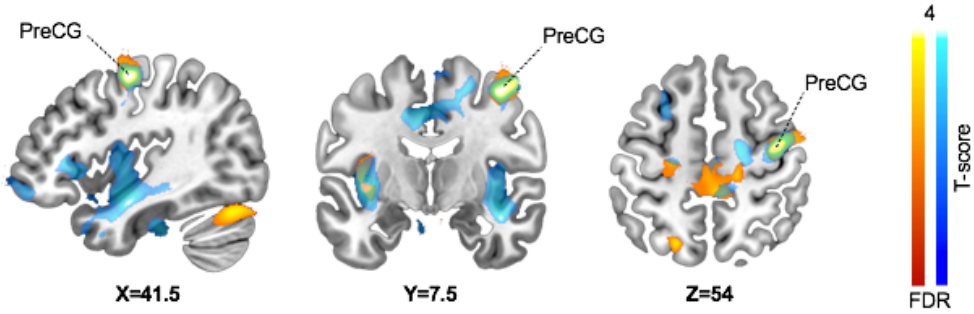


Figure 8. Overlapping (green) brain regions with lower GMV in ASD (red) and Offender groups (blue) compared to control group. The data is FDR-thresholded at $p < 0.01$. PreCG = Precentral Gyrus. The range from FDR correction to T-value of 4 is used for better visualization of the variance in the scale. For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.

1.2. Conclusions

The results demonstrated both distinct and overlapping patterns of structural brain alterations in psychopathy and ASD. Violent offenders exhibited significantly lower GMV in frontotemporal regions implicated in social cognition and emotional empathy compared with individuals with ASD. Compared to healthy controls offender group had widespread lower GMV in frontotemporal and INS areas, while ASD group presented lower GMV in the precuneus and cerebellum. In addition to these divergent patterns, both ASD and offender groups showed a shared GMV reductions in the precentral motor cortex relative to controls. This finding may relate to the shared motor empathy defects in both of the studied disorders.

2. Study II: Aberrant motor contagion of emotions in psychopathy and high-functioning autism

Emotional expressions enable the rapid communication of individuals' internal states and goals to others. Observing emotional expressions in others may automatically engage correspondings behavioral and somatic representation of that emotional state in us trough emotional empathy, whereas cognitive empathy allows us to recognize and understand the emotional state of the other (Blair, 2005b; Dimberg and Thunberg, 1998; Gallese, 2007, 2003; Hatfield et al., 1993; Keysers et al., 2010; Niedenthal, 2007; Wild et al., 2001). Motor empathy in turn, refers to the automatic mimicry of others in social interaction (Blair, 2005a). ASD is associated to defects in cognitive empathy, whereas psychopathy is associated with aberrancies in emotional empathy (Maguire et al., 2024; Murphy et al., 2024).

Study II compared brain basis of facial and vocal expression perception in ASD, psychopathy, and healthy controls. Twenty participans with ASD, 19 violent offender with high psychopatic traits and 19 age-matched controls were scanned

with fMRI during social perception of facial and vocal expressions to investigate the functional differences in the light of the clinical characteristics of these disorders. Face perseption task included dynamic faces with expression of happiness, anger and disgust, while the vocal task included laughter and crying expressions.

2.1. Results

The results revealed that psychopathy was associated with diminished BOLD activity in the motor cortices, cingulate cortex and precuneus to facial (happiness, anger, disgust) and vocal (laughter) emotional expressions in relation to healthy controls. The ROI-analyses indicated a similar effect in sensorimotor (M1, M2, S1, S2) and cingulate cortex (ACC, MCC) during laughter stimulus compared to controls (**Figure 9 and 10**).

In the ASD participants, a similar but less saliently diminished response was observed in relation to laughter (motor cortex) and disgust (motor cortex, cingulate cortex, precuneus) compared to healthy controls. Joy also evoked weaker BOLD responses, but only in cingulate cortex (MCC, ACC) of ASD compared to controls. On the contrary, anger stimuli elicited an enhanced response in precuneus and PCC of ASD group compared to controls. The ROI analyses for ASD versus controls revealed an increased activation of PCC during anger stimulus (**Figure 9 and 10)**.

Direct comparisons between ASD and psychopathy revealed lower activation during laughter (precuneus), joy (motor cortex) and disgust stimuli (motor cortex, precuneus) for psychopathy versus ASD group. The anger stimulus elicited a global deactivation and lower activity compared controls in the psychopathy group as ASD presented an enhanced response compared to controls (precuneus, PCC). This effect was also found in the ROI-analyses with reduced activation of M1, S2, whole motor area, ACC, MCC, and PCC in the psychopathy versus ASD group. No between-groups differences were found for the crying stimulus (**Figure 9 and 10**).

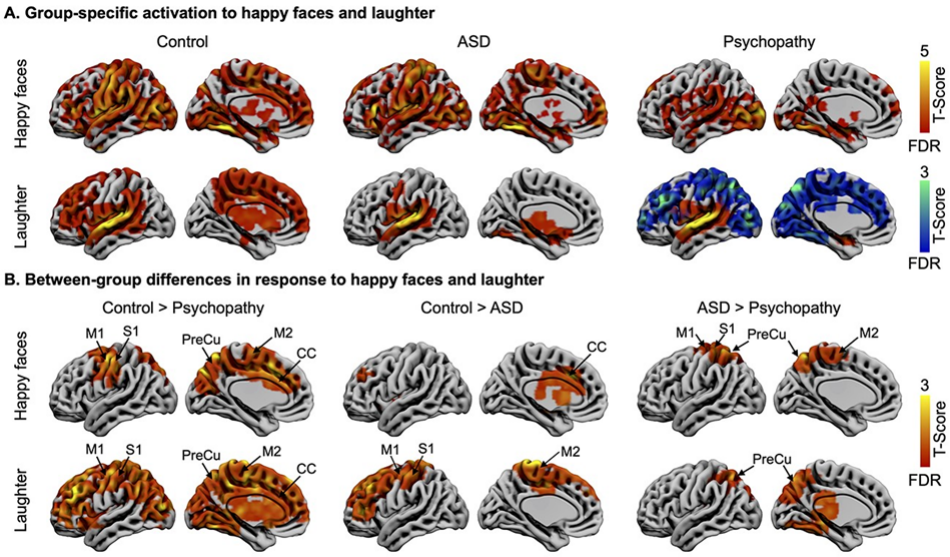


Figure 9. Brain responses to happy faces and social laughter. A) Responses to happy faces and laughter separately for each group. Hot color indicates activation and cool color indicates deactivation. B) Between-group differences in response to happy faces and laughter. Data are thresholded at P < 0.05 with FDR cluster-level correction. CC = Cingulate cortex, S1 = primary somatosensory cortex, S2 = secondary somatosensory cortex, M1 = primary motor cortex, M2 = secondary motor area, and PreCu = precuneus.

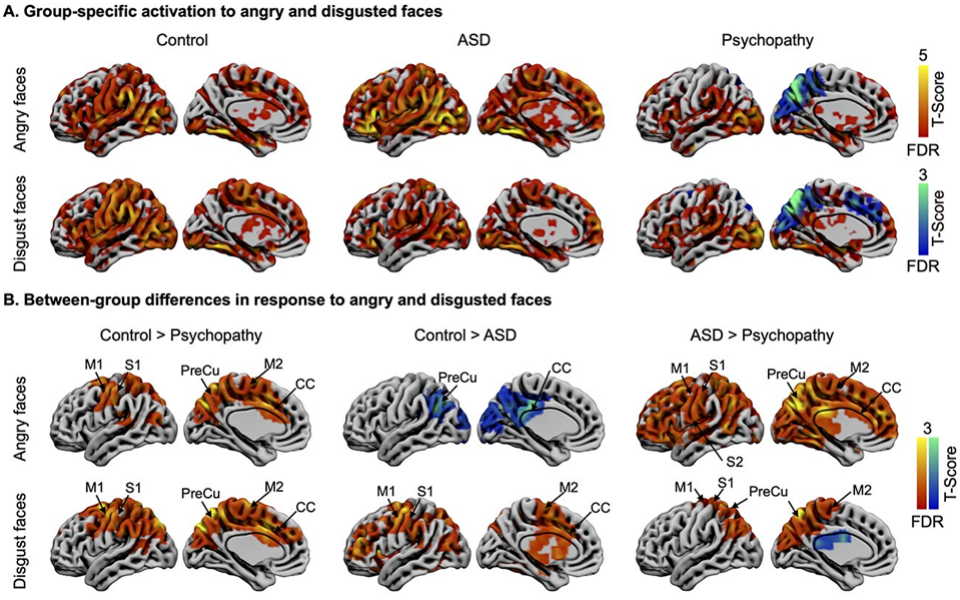


Figure 10. Brain responses to angry and disgusted faces. A) Responses to angry and disgusted faces separately for each group. B) Between-group differences in responses to angry and disgusted faces. Data are thresholded at P < 0.05 with FDR cluster-level correction.

2.2. Conclusions

Psychopathy presented broadly abolished BOLD signal activation, which was lower compared to controls with all stimuli except crying. Similar but more selected and milder findings were seen in the ASD group. Both psychopathy and ASD were characterized by lowered motor cortex responses to laughter and disgust stimuli, whereas anger stimulus elicited contrasting responses from precuneus and PCC compared to controls. Joy stimulus caused a similar lowered response in both disorders, but was localized to the motor cortex, precuneus, cingulate cortex in the offender group and only to the cingulate cortex in the ASD group. There were no significant group differences related to crying stimulus. These findings may relate to deficient empathy processing in psychopathy and ASD.

3. Study III: Aberrant type 2 dopamine and mu-opioid receptor availability in autism spectrum disorder – Abnormal opioid-dopamine interaction in autism

The neurochemical basis of ASD is poorly understood, but previous animal and human studies indicate that neurotransmitters dopamine and endogenous opioids could play a putative role given their involvement in socioemotional processing (Clements et al., 2018; Dichter et al., 2012; Fuccillo, 2016; Kohls et al., 2012; Kosillo and Bateup, 2021; Kyte et al., 2020; Machin and Dunbar, 2011; Oddi et al., 2013; Pavăl and Miclutia, 2021; Pellissier et al., 2018; Tan et al., 2022; Zürcher et al., 2015).

PET-imaging was performed in 16 ASD and 24 control participants to measure D2R availability using radioligand [11C]raclopride and MOR availability using radioligand [11C]carfentanil tracers. Since the there are only few PET-imaging studies on dopamine system functioning in ASD with heterogenous methods and results, the previous striatal dopamine PET-imaging findings were summarized as a meta-analysis to elaborate interpretation of our results in Study III.

3.1. Results

Whole brain voxel-wise analysis did not reveal any group differences for D2R, but ROI-analysis revealed decreased striatal availability in ASD. Post hoc analysis revealed reduced availability in NAcc and globus pallidus of ASD group compared to controls (**Figure 11**). Whole brain voxel-wise analysis for MOR revealed higher availability in precuneus/cuneus and post hoc ROI–analysis revealed lower availability of MOR in hippocampi of the ASD versus control group (**Figure 11**). There was also a significantly weaker regional correlation between D2R and MOR availability in amygdala and NAcc of ASD group compared to controls (**Figure 12**).

The meta-analysis presented a small and heterogenous overall effect of decreased dopamine tracer binding in striatum of ASD compared to controls.

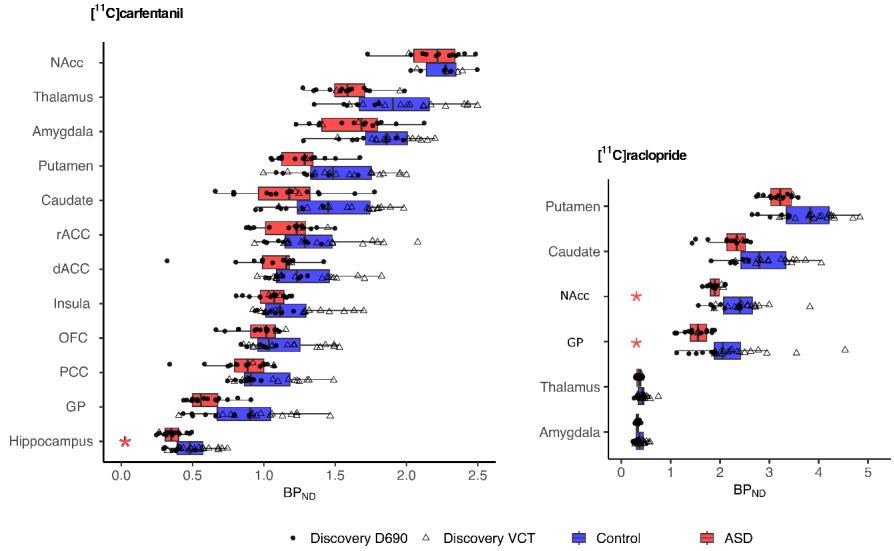


Figure 11. Group-wise binding potentials of [11C]raclopride and [11C]carfentanil BP_{ND} in the predefined ROIs. The blue and red boxes mark the 2nd and 3rd quartiles, with the crossline marking the median of the data. Upper and lower whiskers mark 1.5 interquartile ranges from the box. Data with the two different scanners is marked with circles (Discovery 690) and triangles (Discovery VCT). Significant post hoc differences between the groups are marked with an asterisk. NAcc = Nucleus Accumbens, rACC = rostral anterior cingulate cortex, dACC = dorsal anterior cingulate cortex, OFC = orbitorfrontal cortex, PCC = posterior cingulate cortex, GP = globus pallidus.

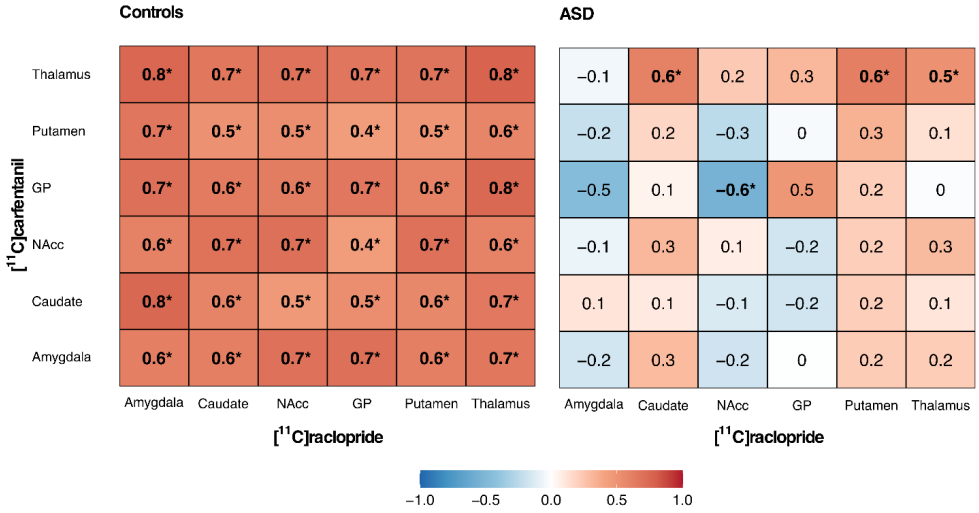


Figure 12. Matrices showing interregional Pearson correlations between [11C]carfentanil (rows) and [11C]raclopride (columns) BP_{ND} in the control and ASD groups. Significant correlations are marked with boldface and asterisk.

3.2. Conclusions

ASD is associated with reduced striatal D2R availability and disrupted interaction between dopaminergic and opioid neurotransmitter systems. These findings may relate to deficient social motivation, reward and pain processing in ASD. Additionally, the study demonstrated preliminary findings of aberrant MOR availability in the cuneus/precuneus and hippocampus areas in ASD compared to controls that could possibly be linked altered opioidergic modulation of the mentalizing network in ASD.

F. Discussion

This thesis presents multimodal comparison of the structural, functional and molecular neural mechanisms behind ASD and psychopathy. We found similar structural and functional deficits in the motor cortex of both disorders, which may relate to reduced motor simulation, motor empathy and emotional contagion. In contrast, psychopathy was associated with structural deficits in the frontotemporal areas related to emotional empathy and more prominent functional deficits in empathy processing areas compared to ASD. Furthermore, the perception of anger elicited differential responses in the mentalizing network in ASD and psychopathy, suggesting contrasting emotional processing in these disorders. Moreover, ASD was associated with lower dopamine 2 receptor binding in the striatum with additional uncoupling to the opioid system. These findings may reflect a dysfunctional social motivation, reward and pain mechanisms in ASD.

1. Impaired empathy mechanisms as a unifying factor for psychopathy and ASD

Anatomical aberrancies of the motor cortex and deficient motor functioning are early signs of ASD and work also as a predictor of outcome in this disorder (Eigsti, 2013; Fournier et al., 2010; Mosconi et al., 2006; Mosconi and Sweeney, 2015; Mostofsky et al., 2007; Nebel et al., 2014, 2012; Riddle et al., 2017). There are also some findings indicating poor motor control and deficits of the motor cortex in psychopathy and conduct disorder (De Brito et al., 2019, 2021b; Murphy, 2007; Robinson and Bresin, 2014; Tillem et al., 2019). Our structural MRI finding showing shared motor cortex defect in psychopathy and ASD could be related to the similarities in aberrant motor functioning, but even more evidently to similarities in higher-order social cognition aspects such as motor simulation and motor empathy (Bhattacharjee et al., 2021; Bons et al., 2013; Carnevali et al., 2024; Eigsti, 2013; Helt et al., 2021; Khvatskaya and Lenzenweger, 2016; Mier et al., 2014; Tomasino and Gremese, 2016). This relation to deficient motor empathy and motor simulation is further supported with our findings indicating weaker fMRI activity

in the motor cortex during laughter and disgust perception in both psychopathy and ASD (Caspers et al., 2010; Gallese, 2003; Niedenthal, 2007; Tomasino and Gremese, 2016).

Lower GMV in the offender versus ASD group in the right temporal pole and left IFG areas might relate to emotional empathy which aligns with the clinical findings of emotional empathy deficits in psychopathy, but not in ASD (Leigh et al., 2013; Maguire et al., 2024; Murphy et al., 2024; Sato and Uono, 2019). Moreover, the ROI analyses suggested even broader involvement of the frontotemporal areas related to social cognition and empathy in psychopathy compared to ASD (Hogeveen et al., 2016; Leigh et al., 2013; Shamay-Tsoory et al., 2009).

The lower BOLD responses to disgust, joy, anger and laughter stimuli in sensorimotor cortex and cingulate cortex, may reflect a broader deficiency of empathy mechanisms in psychopathy compared to ASD (Dimberg and Thunberg, 1998; Gallese, 2003; Hatfield et al., 1993; Mier et al., 2014; Niedenthal, 2007; Wild et al., 2001). The sensorimotor and cingulate cortices are critically involved in social perception and together with INS they contribute to embodied simulation and emotional contagion (Arioli and Canessa, 2019; Caspers et al., 2010; Fusar-Poli et al., 2009; Gallese, 2007; Hogeveen et al., 2016; Keysers et al., 2010; Mende-Siedlecki et al., 2013; Niedenthal, 2007; Tomasino and Gremese, 2016). Embodied simulation and emotional contagion refer to the automatic process of recreating other´s actions, sensations and emotions in observers own central nervous system and are closely related to emotional and motor empathy (Blair, 2005a; Gallese, 2007, 2003; Hatfield et al., 1993; Keysers et al., 2010; Niedenthal, 2007; Nummenmaa et al., 2008; Oliver et al., 2018; Tomasino and Gremese, 2016). Meta-analyses of previous studies on psychopathy have found lower activation of ACC in face processing tasks, but no alterations in sensorimotor cortex (Penagos-Corzo et al., 2022).

Findings in ASD group are indicative of similar but less severely disrupted contagion and embodiment of emotions, particularly for disgust and laughter stimuli. The lowered activation for happy stimuli in ACC and MCC suggests further dysfunction of empathy related areas in ASD group compared to controls but milder than in the offender group (Arioli et al., 2021a; Fan et al., 2011). fMRI meta-analyses of ASD and face processing have previously presented a lower activation of the cingulate cortex, but higher activation in the precuneus and no group differences in the motor cortex (Di Martino et al., 2009; Patriquin et al., 2016).

Previous studies have found impairments in the embodied simulation of emotions and actions in ASD, but also in psychopathy (Eigsti, 2013; Mier et al., 2014). Motor empathy and automatic mimicry are impaired in both ASD and psychopathy, and closely relate to emotional contagion and embodied simulation (Ayache et al., 2025; Bons et al., 2013; Eigsti, 2013; Harmsen, 2019; Helt et al., 2021; Khvatskaya and Lenzenweger, 2016; McIntosh et al., 2006; Mier et al., 2014; Oberman et al., 2009). Subjects with ASD and psychopathy had lower activation in

general areas of empathy processing (ACC) and cognitive empathy (MCC), rather than in areas involved in emotional empathy (Arioli et al., 2021a, 2021b; Chen et al., 2022; Fallon et al., 2020; Fan et al., 2011; Nummenmaa et al., 2008; Oliver et al., 2018).

In contrast to our structural findings, the fMRI results do not support a clear dissociation of impaired emotional empathy in psychopathy and impaired cognitive empathy in autism spectrum disorder (ASD), but instead indicate a more general disruption of empathy-related networks in both conditions. Additionally, and contrary to expectations, both disorders presented also aberrancies in ToM processing related areas, namely the precuneus and PCC (Mars et al., 2012; Schilbach et al., 2008).

2. Dysfunctional social reward, motivation and pain in the atypical development of empathy in ASD

Animal and human studies have suggested that dopamine dysregulation is related to the dysfunction of the social motivation and reward system in ASD (Chevallier et al., 2012; Clements et al., 2018; Kohls et al., 2012; Pavăl, 2017; Tan et al., 2022; Zürcher et al., 2015). In light of these previous theories and findings, our PET-imaging results of lower striatal dopamine 2 receptor availability may reflect aberrant social motivation and reward function in ASD, but possibly also broader dysfunction of the reward system.

Animal studies have suggested an interregulatory relationship between dopamine and opioid systems, which is also manifested as a positive correlation between dopamine synthesis and MOR binding in human PET-studies (Colasanti et al., 2012; Escobar et al., 2020; Majuri et al., 2018; Margolis et al., 2014; Mick et al., 2014; Rada et al., 2010; Wiskerke et al., 2011). In line with these suggestions, a strong correlation between [11C]raclopride and [11C]carfentanil binding was observed in the control group. However, similar correlation between the receptor systems in the ASD was only found in the thalamus. The regional correlation of MOR and D2R binding was significantly stronger in the amygdala and NAcc of the control group compared to ASD. Along with dopamine, also endogenous opioids are associated with modulation of social motivation and reward, whereas NAcc is considered as an essential brain region for the interaction between these two neurotransmitter systems (Chelnokova et al., 2014; Kohls et al., 2012; Loseth et al., 2014; Vanderschuren et al., 2016).

Pain sensation modulation is also linked with dopamine and opioid systems in NAcc (Hagelberg et al., 2002; Harris and Peng, 2020). While sensory abnormalities are central to ASD, studies to date have provided only limited information on pain modulation in ASD (Bogdanova et al., 2022). Social pain refers to the distressing emotional experience that follows social rejection or loss and shares its neural basis

with physical pain (Cacioppo et al., 2011; Eisenberger, 2012; MacDonald and Leary, 2005). Both sensory and social pain are modulated by the endogenous opioid system and their sensitivities have been shown to be related (Eisenberger, 2012; Hsu et al., 2013; Kyte et al., 2020; Machin and Dunbar, 2011). There is also an overlap between the brain areas related to pain and empathy with connections also to NAcc and opioidergic modulation (Bernhardt and Singer, 2012; Fallon et al., 2020; Timmers et al., 2018). In addition to social motivation and reward, our PET-imaging finding may be related to atypical experiencing of social pain in ASD.

Since social impairments are present also in other neuropsychiatric disorders, the present findings of dopaminergic dysfunction may not be specific to ASD (Fernandes et al., 2018; Green et al., 2015; Huey et al., 2006; Magno et al., 2022; Plavén-Sigray et al., 2022; Schilbach, 2016). For instance, impairments in social cognition are present in schizophrenia, which has been associated with lower dopamine receptor availability in the thalamus (Fernandes et al., 2018; Green et al., 2015; Plavén-Sigray et al., 2022). Interestingly, Lukkarinen et al. found lower striatal D2R availability in violent offenders versus controls (Lukkarinen et al., 2024). Together with this finding, our results may reflect the tendency for impulsive aggressive behavior also in ASD (Buckholtz et al., 2010b; Burghart et al., 2024; De Brito et al., 2021a; Hill et al., 2014; Jambroes et al., 2018; Kanne and Mazurek, 2011; Schlüter et al., 2013; Seo et al., 2008; Tonizzi et al., 2022; Volkow et al., 2009).

In our fMRI study, anger elicited increased activation of PCC and precuneus in ASD, but these areas showed decreased activation in psychopathy compared to controls. Fears and phobias are more prevalent in ASD than in typically developing children (Lydon et al., 2015), whereas fearlessness and low responsiveness to threat are characteristic to psychopathy (Dugré et al., 2020; Maguire et al., 2024). Our finding suggests hypersensitivity to a threatening stimuli of angry faces in ASD, as demonstrated by a previous study (Krysko and Rutherford, 2009), whereas psychopathy showed evidence of hyposensitivity to expressions of anger. These disorder specific atypical responses in the areas of task-negative DMN could reflect dysfunctional emotional processing and ToM related to fear in ASD and psychopathy (Padmanabhan et al., 2017; Smitha et al., 2017; Sreenivas et al., 2012). These findings may also reflect the differences in reactive and proactive aggression with ASD and psychopathy (De Brito et al., 2021a; Jambroes et al., 2018; Kirst et al., 2022; Oubrahim and Combalbert, 2021; Pouw et al., 2013).

In sum, our data suggest that ASD and psychopathy share structural and functional deficits in the motor cortex that are possibly related to empathy, and more specifically to emotional contagion and embodied simulation (Blair, 2005a; Gallese, 2007; Hatfield et al., 1993; Niedenthal, 2007; Tomasino and Gremese, 2016). We found structural deficits of emotional empathy brain areas in psychopathy compared to ASD, but our fMRI findings do not support the idea of fine cut distinction between emotional and cognitive empathy impairments in these

disorders (Fan et al., 2011; Leigh et al., 2013; Sato and Uono, 2019). However, our results suggest a more severely impaired structural and functional mechanisms of empathy in psychopathy compared to ASD (Arioli et al., 2021a; Chen et al., 2022; Fallon et al., 2020; Fan et al., 2011; Hogeveen et al., 2016; Leigh et al., 2013; Shamay-Tsoory et al., 2009).

Additionally, ASD was associated with reduced striatal dopamine 2 receptor availability with altered opioidergic connection suggesting an aberrant functioning of the social motivation, reward and pain mechanisms (Bernhardt and Singer, 2012; Chevallier et al., 2012; Clements et al., 2018; Kohls et al., 2012). Empathy is motivated behavior and modulates the rewarding value of social interaction, such as mimicry (Ferguson et al., 2020; Gossen et al., 2014; Hsu et al., 2018b; Neufeld and Chakrabarti, 2016; Sims et al., 2012; Weisz and Zaki, 2018). In ASD the socially rewarding effect of mimicry and being imitated is impaired (Hsu et al., 2018a; Neufeld et al., 2019). The dysfunctional dopaminergic and opioidergic neurotransmitter mechanisms may maintain a vicious circle of reduced social reward resulting in lack of motivation for empathetic engagement, leading again to more reduced social reward (Gossen et al., 2014; Hsu et al., 2018b; Neufeld and Chakrabarti, 2016; Weisz and Zaki, 2018). These mechanisms may further lead to atypical development of the underlying neural systems of empathy in ASD.

Similarities between aberrant striatal dopamine 2 receptor binding in ASD and psychopathy may suggest shared neurotransmitter mechanisms potentially associated with social reward and motivation but also with impulsive aggression (Buckholtz et al., 2010a; Foulkes et al., 2014a, 2014b; Glenn and Yang, 2012; Lukkarinen et al., 2024). Despite the established genetic links between psychopathy and ASD, these overlapping anatomical, functional and neurochemical mechanisms most likely reflect different kind of aberrant developmental trajectories and neuropathological etiologies leading to these contrasting phenotypes of social cognition disorders (Anderson and Kiehl, 2014; Beopoulos et al., 2022; Eric Courchesne et al., 2011; Gao et al., 2009; Gur, 2005; Junewicz and Billick, 2020; Lord et al., 2020; Oostermeijer et al., 2016; Raine et al., 2003; Tiihonen et al., 2020; Yang et al., 2015). Differences in the dopamine dysregulation, and how it is connected to impaired empathy in psychopathy and ASD, could possibly explain these differences in the phenotypes. However, further investigation is needed.

3. Clinical implications

Automatic mimicry and deliberate imitation are essential for the development of human empathy and involve the same brain areas (Benuzzi et al., 2023; Braadbaart et al., 2014; Carr et al., 2003; Coplan and Goldie, 2011; Hatfield et al., 1993; Holland et al., 2021; Iacoboni, 2009; Niedenthal, 2007; Prochazkova and Kret, 2017). Therapeutic approaches utilizing imitation to promote mimicry and prosocial

behavior in ASD have been studied for several decades with good results (DeJesus et al., 2020; Ingersoll et al., 2017; Krupicz, 2014; Ta and Mj, 2011). However, there are only few studies on the applicability of these approaches in therapeutic treatment of psychopathy and callous unemotional traits, but the results have been promising (Dadds et al., 2012; Kimonis et al., 2019; Kyranides et al., 2023). Based on our findings, further research on the use of imitative therapeutic techniques as an early intervention to promote prosocial behavior trough emotional and motor empathy in both disorders is warranted.

Impaired empathy processing may constitute a predisposing factor to aggressive behavior in people with ASD and psychopathy (Pouw et al., 2013; Romero-Martínez et al., 2022; Winter et al., 2017). We found that psychopathy was associated with more prominent structural and functional impairments especially in the brain areas related to emotional empathy, which may explain the more antisocial and violent phenotype in psychopathy versus to ASD. Reactive aggression is positively correlated with affective empathy in ASD and promoting cognitive empathy is even more important in reducing aggressive behavior in this population, but the research in this area is still scarce (Dandil et al., 2020; Pouw et al., 2013).

Our PET data provided evidence on dopaminergic but also opioidergic dysregulation, which may relate to impaired social motivation, reward and pain mechanisms in ASD (Chevallier et al., 2012; Clements et al., 2018; Kohls et al., 2012; Kyte et al., 2020; Machin and Dunbar, 2011; Pavăl and Miclutia, 2021). Since reduced [11C]raclopride BP_{ND} and D2R availability can reflect either hypo- (low receptor density) or hyperdopaminergic tone (high endogenous agonists occupancy), the exact mechanisms for possible pharmacologic interventions to treat ASD symptoms cannot be determined based on the present findings (Innis et al., 2007; Laruelle, 2000a, 2000b; Walker, 2008). However, the ASD core symptoms have been associated to both hypo- and hyperdopaminergic alterations in animals and humans (Blum et al., 2024; Kosillo and Bateup, 2021; Pavăl, 2017; Pavăl and Miclutia, 2021). In addition, it has been proposed that social and sensory defects would be related to dysfunction of the mesocorticolimbic dopaminergic circuit, while restricted repetitive behavior would relate to nigrostriatal dopaminergic circuit (Blum et al., 2024; Kosillo and Bateup, 2021; Pavăl, 2017; Pavăl and Miclutia, 2021).

Dopamine is also one of the key neurotransmitters behind aggressive behavior comorbid in ASD (Hill et al., 2014; Kanne and Mazurek, 2011; Narvaes and Martins de Almeida, 2014; Padilla-Coreano and Martínez-Rivera, 2025; Seo et al., 2008). Antipsychotic dopamine antagonists and opioid antagonists alleviate hyperactivity, irritability and restricted repetitive behavior in ASD but may have negative effect on social motivation (Costello et al., 2024; Deb et al., 2023; Meza et al., 2022). A meta-analysis has revealed risperidone and aripiprazole as the most effective antipsychotics in the treatment of aggression in ASD (Fung et al., 2016). Dopaminergic stimulant medication and dopamine agonists restore motivation in

neurodegenerative disorders and schizophrenia and acute low doses of stimulant drugs are shown to enhance the value of social rewards in neurotypical adults, but they are linked with aggressive social behavior and their effects on the core symptoms of ASD are largely unknown (Barnard-Brak et al., 2016; Bershad and de Wit, 2025; Costello et al., 2024; Maoz et al., 2014; Osugo et al., 2022; Seo et al., 2008). Overall, the relationship between dopamine and symptoms of ASD appears to be multifaceted but may be explained by a more global dysregulation of dopaminergic systems.

Opioid antagonists may also alleviate hyperactivity and restlessness in ASD, but they have a negative effect on social reward (Inagaki et al., 2020; Løseth et al., 2024; Roy et al., 2015; Wardle et al., 2016). Acute administration of opioid agonists in turn reduces responses to negative facial expressions such as anger and feelings of social rejection and increase the value of social reward in humans (Bershad and de Wit, 2025). Relatedly, clinical studies have shown that opiate addicts in maintenance treatment in turn display deficits in social inference, emotion recognition and ToM (Eidenmueller et al., 2021; Gandolphe et al., 2018; McDonald et al., 2013; Yazgeç et al., 2023).

The novel dopamine partial agonists offer a promising means for treating dopamine dysregulation, as they are proposed to stabilize the dopaminergic tone trough their effect on post synaptic and presynaptic dopamine receptors (Mandic-Maravic et al., 2022; Stahl, 2001). Additionally, these dopamine system stabilizers decrease negative symptoms of schizophrenia, which significantly overlap with the social symptoms of ASD, including social motivation and reward (Mandic-Maravic et al., 2022; Osugo et al., 2022; Trevisan et al., 2020). Despite their good tolerability and their promising mechanisms to treat dopamine dysregulation, there are currently only studies on aripiprazole to treat the behavioral symptoms of ASD (Mandic-Maravic et al., 2022; Mohr et al., 2022).

Oxytocin modulates social motivation and reward through its effect on dopaminergic and opioidergic circuits and its exogenous administration has been found to enhance social cognition in healthy adults (Dal Monte et al., 2025; Keech et al., 2018; MacDonald and MacDonald, 2010; Stavropoulos and Carver, 2013; Walsh et al., 2023). However, the effects of oxytocin on social cognition in ASD have thus far been modest and mixed (Audunsdottir et al., 2024; Huang et al., 2021; Keech et al., 2018). The dopaminergic and opioidergic dysregulation may possibly modify the effect of oxytocin in ASD and explain these surprisingly poor results, but further investigation is needed on this issue.

Based on our results and current scientific literature, more research is still needed on the effects of dopaminergic medication (stimulants, dopamine agonists, dopamine partial agonists) to social cognition in promoting prosocial behavior in ASD. Additionally, there is a need for research on the possible positive effect of novel dopamine receptor partial agonists (cariprazine and brexpipratzole) to repetitive and aggressive behavior in ASD.

4. Strenghts and limitations

There are only few previous imaging studies comparing psychopathy and ASD and our multimodal imaging work shed important novel insights on their relationship. In contrast with many other studies, we managed to collect a clinical sample of individuals with ASD and psychopathy and did not study the traits in neurotypical population like previous studies. Additionally, our Study III is first multi-ligand study measuring the dopamine and opioid systems and their relations in ASD. However, since our studies were cross-sectional and restricted to adults, no causal links between our findings and clinical symptoms associated with these disorders can be established and longitudinal studies are needed.

Despite the limited sample size, we established robust group differences and correlations to the symptoms of psychopathy and ASD. The participants were matched by their age and sex, but there was statistical differences in their educational background between groups. Lower intellectual ability is a possible confounding factor in ASD and psychopathy and a formal evaluation of IQ in the future studies is recommended (Elsabbagh et al., 2012; Sánchez De Ribera et al., 2019). As we included only male participants, our results do not represent ASD and psychopathy population as a whole and more studies on women are needed (Lai et al., 2015; Tully et al., 2023b).

Even though the offenders were recruited from a strictly controlled prison environment and there was no evidence of current alcohol or drug abuse in our thorough clinical testing for any participants, the more prevalent abuse history in the offender group is a possible confounding factor in Studies I and II. Additionally, the use of psychoactive medicine could not be totally limited in any of the studies and has to be considered as a possible confounding factor especially for the functional and neurotransmitter measurements (Bonhomme and Esposito, 1998; H. Roder et al., 2010; Wandschneider and Koepp, 2016). However, we managed to control the use of most confounding dopaminergic and opioidergic medications in the ASD group for the Study III.

We were able to compare the interpersonal/affective and lifestyle/antisocial factors of psychopathy with PCL-R measures in the offender group, but a comparative non-psychopatic forensic sample would be ideal for determining the effects of psychopathy from the mere antisocial personality disorder effect on the results (Raine, 2018). Although the comorbidity of psychopathy and ASD is possible we did not execute a formal ADOS-2 and PCL-R evaluations across the groups, but only measured their traits with relatively unreliable self-report questionnaires (Kelsey et al., 2015; Maguire et al., 2024; Murphy et al., 2024; Rogers et al., 2006; Wigham et al., 2019). However, there was only one offender participant who had high autism traits but without clinically relevant ASD symptoms in our sample. In addition to considering criminal autistic psychopathy as a possible confounding factor, the more formal diagnostics of these disorders

across the sample could also serve further research on this unexplored territory (Maguire et al., 2024; Murphy et al., 2024). Additionally, behavioral measurement of emotional/cognitive empathy, reactive/proactive aggression, and alexithymia across the study groups would have helped the clinical interpretation of the neuroimaging results (Ayache et al., 2025; Baron-Cohen and Wheelwright, 2004; Bird and Viding, 2014; Brugman et al., 2017; Davis, 2011; De Brito et al., 2021a; Franz et al., 2021; Leising et al., 2009; Lockwood et al., 2013; Maguire et al., 2024; Pouw et al., 2013).

In the light of our results, measuring spontaneous automatic mimicry with EMG simultaneously with the fMRI tasks, would have been a beneficial additional method to study the imitative and motor empathy aspects of emotional contagion and embodied simulation in these disorders (McIntosh et al., 2006; Oberman et al., 2009).

Since [11C]raclopride binds to D2R/D3R and [11C]carfentanil binds specifically to MOR, our results cannot reveal the role of other dopamine and opioid receptor types (e.g. D1R, DOR, KOR). in psychopathy and autism. For example, D1R and D2R play opposing roles in reward and aversive learning and comparing their availability in ASD and psychopathy might be enlightening in the future studies (Blair et al., 2004; Cox et al., 2015; Schuetze et al., 2017; Soares-Cunha et al., 2016). Additionally, [11C]raclopride measures receptor availability reliably only in the striatum and presents no relevant information of the extra-striatal dopaminergic aberrancies also presented in ASD (Murayama et al., 2022; Svensson et al., 2019). Finally, our single baseline scans reflect predominantly tonic receptor availabilities and do not reveal any precise dopaminergic or opioidergic neurotransmitter mechanisms behind them (e.g. postsynaptic/presynaptic, hypo-/hyperdopaminergic or opioidergic function) (Alakurtti et al., 2015; Hirvonen et al., 2009; Laruelle, 2000b). Comparing basal and phasic task-related availabilities would provide more detailed functional information of these neurotransmitter systems and their interaction in ASD, but also in psychopathy.

The use of two different PET-scanner in Study III may contribute to data variability and influence the results. However, we attempted to statistically control these differences by modelling a random intercept for each scanner. Due to the heterogenous methodology in the included studies, our meta-analysis provides only a general overview on the striatal dopaminergic aberrancies in ASD.

G. Conclusions and future perspectives

1. ASD and psychopathy are both associated with structural and functional changes in the motor areas, possibly reflecting the dysfunctional embodied simulation and emotional contagion of empathy processing. These impairments were more prominent in psychopathy.
2. Frontotemporal structural aberrancies in the brain areas related to social cognition and emotional empathy differentiate psychopathy from ASD.

3. Cerebral processing of anger differs between psychopathy and ASD possibly in relation to their differences in mentalizing processes.
4. ASD is associated with striatal dopaminergic dysregulation with altered endogenous opioid system interaction. This finding could reflect dysfunctional social motivation, reward and pain leading to reduced empathy responses and maldevelopment of the underlying brain mechanisms.

Future longitudinal neuroimaging studies are required to define the developmental aspects of psychopathy and ASD. Developmental trajectory of ASD has been recently mapped in detail, but comparable research in conduct disorder and psychopathy has been more limited (Boedhoe et al., 2020; Eric Courchesne et al., 2011; Oostermeijer et al., 2016; Van Rooij et al., 2018; Yang et al., 2015). Imaging studies in the early childhood with long follow up times might help in delineating the pathoetiological neural mechanisms behind the origin of these disorders. Comparative imaging studies with children and adolescents with callous unemotional or autistic traits might also be beneficial in studying the altered developmental trajectories of social cognition (Klapwijk et al., 2016; O'Nions et al., 2014).

Comparing autism and psychopathy using fMRI in more naturalistic social simulations tasks, such as movie viewing or mentalizing/empathy tasks, could be useful in finding clinical relevance to the differing empathy impairments (Lenzen et al., 2021; Nummenmaa et al., 2021; Philip et al., 2012; Schulte-Rüther et al., 2011; Sugranyes et al., 2011; Tholen et al., 2020; Winter et al., 2017). Considering current literature and our contrasting findings related to DMN, a comparative connectivity analysis with rs-fMRI imaging could provide important information on the differences of ToM processing in psychopathy and ASD (Cohn et al., 2015; Espinoza et al., 2019; Lau et al., 2020, 2019; Philippi et al., 2015; Umbach and Tottenham, 2021; Wang et al., 2021; W. Wang et al., 2018; Winters et al., 2021).

PET imaging and fMRI combined with pharmacological challenges using dopamine and opioid antagonists or stimulants in studying dopamine and opioid systems and their dysfunctional inter-regulation, would give a more profound understanding on the possibly treatable mechanisms behind ASD symptoms (Dal Monte et al., 2025; Drevets et al., 2001; Fathabadipour et al., 2022; Massaccesi et al., 2024; Tully et al., 2023c; Zürcher et al., 2021). A direct PET-imaging comparison between psychopathy and ASD with different dopamine tracers (D2R, D1R, FDOPA, DAT) might be useful in defining more precise and disorder specific dysregulatory mechanisms for possible treatment targets in both disorders. Finally, combining dopamine tracer PET-imaging and fMRI during mentalizing/empathy tasks may clarify the connections between empathy and reward systems in these phenotypically contrasting disorders, but also in neurotypical.

References

Adams, A.G., Schweitzer, D., Molenberghs, P., Henry, J.D., 2019. A meta-analytic review of social cognitive function following stroke. Neurosci Biobehav Rev 102, 400–416. https://doi.org/10.1016/j.neubiorev.2019.03.011

Adolphs, R., 2001. The neurobiology of social cognition. Current Opinion in Neurobiology 11, 231–239. https://doi.org/10.1016/S0959-4388(00)00202-6

Alakurtti, K., Johansson, J.J., Joutsa, J., Laine, M., Bäckman, L., Nyberg, L., Rinne, J.O., 2015. Long-term test–retest reliability of striatal and extrastriatal dopamine D2/3 receptor binding: study with [11C]raclopride and high-resolution PET. J Cereb Blood Flow Metab 35, 1199–1205. https://doi.org/10.1038/jcbfm.2015.53

Allely, C.S., Wilson, P., Minnis, H., Thompson, L., Yaksic, E., Gillberg, C., 2017. Violence is Rare in Autism: When It Does Occur, Is It Sometimes Extreme? The Journal of Psychology 151, 49–68. https://doi.org/10.1080/00223980.2016.1175998

Alvares, G.A., Bebbington, K., Cleary, D., Evans, K., Glasson, E.J., Maybery, M.T., Pillar, S., Uljarević, M., Varcin, K., Wray, J., Whitehouse, A.J., 2020. The misnomer of 'high functioning autism': Intelligence is an imprecise predictor of functional abilities at diagnosis. Autism 24, 221–232. https://doi.org/10.1177/1362361319852831

Álvarez-Couto, M., García-Villamisar, D., del Pozo, A., n.d. Callous unemotional traits mediate the presence of challenging behaviors in adults with autism spectrum disorder and intellectual disability. Int J Dev Disabil 70, 1237–1244. https://doi.org/10.1080/20473869.2023.2171756

Amaral, D.G., Schumann, C.M., Nordahl, C.W., 2008. Neuroanatomy of autism. Trends in Neurosciences 31, 137–145. https://doi.org/10.1016/j.tins.2007.12.005

American Psychiatric Association. (1952). Diagnostic and statistical manual of mental disorders (1st ed.).

American Psychiatric Association. (1980). Diagnostic and statistical manual of mental disorders (3rd ed.).

American Psychiatric Association. (1987). Diagnostic and statistical manual of mental disorders (3rd ed., rev.).

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.). https://doi.org/10.1176/appi.books.9780890420614.dsm-iv

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Amodio, D.M., Frith, C.D., 2006. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 7, 268–277. https://doi.org/10.1038/nrn1884

Anderson, N.E., Kiehl, K.A., 2014. Psychopathy: Developmental perspectives and their implications for treatment. Restorative Neurology & Neuroscience 32, 103–117. https://doi.org/10.3233/RNN-139001

Aoki, Y., Cortese, S., Tansella, M., 2015. Neural bases of atypical emotional face processing in autism: A meta-analysis of fMRI studies. World J Biol Psychiatry 16, 291–300. https://doi.org/10.3109/15622975.2014.957719

Aoki, Y., Inokuchi, R., Nakao, T., Yamasue, H., 2014. Neural bases of antisocial behavior: a voxel-based meta-analysis. Social Cognitive and Affective Neuroscience 9, 1223–1231. https://doi.org/10.1093/scan/nst104
Ardila, A., Bernal, B., Rosselli, M., 2018. Executive Functions Brain System: An Activation Likelihood Estimation Meta-analytic Study. Archives of Clinical Neuropsychology 33, 379–405. https://doi.org/10.1093/arclin/acx066
Ariens, E.J., 1954. Affinity and intrinsic activity in the theory of competitive inhibition. I. Problems and theory. Arch Int Pharmacodyn Ther 99, 32–49.
Arioli, M., Canessa, N., 2019. Neural processing of social interaction: Coordinate-based meta-analytic evidence from human neuroimaging studies. Hum Brain Mapp 40, 3712–3737. https://doi.org/10.1002/hbm.24627
Arioli, M., Cattaneo, Z., Ricciardi, E., Canessa, N., 2021a. Overlapping and specific neural correlates for empathizing, affective mentalizing, and cognitive mentalizing: A coordinate-based meta-analytic study. Human Brain Mapping 42, 4777–4804. https://doi.org/10.1002/hbm.25570
Arioli, M., Gianelli, C., Canessa, N., 2021b. Neural representation of social concepts: a coordinate-based meta-analysis of fMRI studies. Brain Imaging and Behavior 15, 1912–1921. https://doi.org/10.1007/s11682-020-00384-6
Ashburner, J., Friston, K.J., 2000. Voxel-Based Morphometry—The Methods. NeuroImage 11, 805–821. https://doi.org/10.1006/nimg.2000.0582
Atzil, S., Touroutoglou, A., Rudy, T., Salcedo, S., Feldman, R., Hooker, J.M., Dickerson, B.C., Catana, C., Barrett, L.F., 2017. Dopamine in the medial amygdala network mediates human bonding. Proc. Natl. Acad. Sci. U.S.A. 114, 2361–2366. https://doi.org/10.1073/pnas.1612233114
Audunsdottir, K., Sartorius, A.M., Kang, H., Glaser, B.D., Boen, R., Nærland, T., Alaerts, K., Kildal, E.S.M., Westlye, L.T., Andreassen, O.A., Quintana, D.S., 2024. The effects of oxytocin administration on social and routinized behaviors in autism: A preregistered systematic review and meta-analysis. Psychoneuroendocrinology 167, 107067. https://doi.org/10.1016/j.psyneuen.2024.107067
Ayache, J., Stevenson, N., Patel, E., Sumich, A., Dumas, G., Heym, N., 2025. A “fine-cuts” approach disentangling psychopathic, autistic and alexithymic traits in their associations with affective, cognitive and motor empathy. Personality and Individual Differences 246, 113279. https://doi.org/10.1016/j.paid.2025.113279
Bak, M., Weltens, I., Bervoets, C., De Fruyt, J., Samochowiec, J., Fiorillo, A., Sampogna, G., Bienkowski, P., Preuss, W.U., Misiak, B., Frydecka, D., Samochowiec, A., Bak, E., Drukker, M., Dom, G., 2019. The pharmacological management of agitated and aggressive behaviour: A systematic review and meta-analysis. Eur Psychiatry 57, 78–100. https://doi.org/10.1016/j.eurpsy.2019.01.014
Baldassarre, A., Filardi, M.S., Spadone, S., Penna, S.D., Committeri, G., 2021. Distinct connectivity profiles predict different in-time processes of motor skill learning. NeuroImage 238, 118239. https://doi.org/10.1016/j.neuroimage.2021.118239
Bandelow, B., Wedekind, D., 2015. Possible role of a dysregulation of the endogenous opioid system in antisocial personality disorder. Hum Psychopharmacol 30, 393–415. https://doi.org/10.1002/hup.2497
Barchi-Ferreira, A., Osório, F., 2021. Associations between oxytocin and empathy in humans: A systematic literature review. Psychoneuroendocrinology 129, 105268. https://doi.org/10.1016/j.psyneuen.2021.105268

Barnard-Brak, L., Davis, T.N., Schmidt, M., Richman, D.M., 2016. Effects associated with on- and off-label stimulant treatment of core autism and ADHD symptoms exhibited by children with autism spectrum disorder. Developmental Neurorehabilitation 19, 46–53. https://doi.org/10.3109/17518423.2014.904949
Barnard-Brak, L., Richman, D.M., 2021. Autistic and Psychopathic Traits among a Community-based Sample of Adults. Deviant Behavior 42, 950–957. https://doi.org/10.1080/01639625.2019.1706357
Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C., Williams, S.C.R., 2000. The amygdala theory of autism. Neuroscience & Biobehavioral Reviews 24, 355–364. https://doi.org/10.1016/S0149-7634(00)00011-7
Baron-Cohen, S., Wheelwright, S., 2004. The Empathy Quotient: An Investigation of Adults with Asperger Syndrome or High Functioning Autism, and Normal Sex Differences. J Autism Dev Disord 34, 163–175. https://doi.org/10.1023/B:JADD.0000022607.19833.00
Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E., 2001. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Malesand Females, Scientists and Mathematicians. J Autism Dev Disord 31, 5–17. https://doi.org/10.1023/A:1005653411471
Basu, S., Kwee, T.C., Surti, S., Akin, E.A., Yoo, D., Alavi, A., 2011. Fundamentals of PET and PET/CT imaging. Annals of the New York Academy of Sciences 1228, 1–18. https://doi.org/10.1111/j.1749-6632.2011.06077.x
Beard, R., Stucki, A., Schmitt, M., Py, G., Grundschober, C., Gee, A.D., Tate, E.W., 2018. Building bridges for highly selective, potent and stable oxytocin and vasopressin analogs. Bioorganic & Medicinal Chemistry, Tetrahedron young Investigator Award 26, 3039–3045. https://doi.org/10.1016/j.bmc.2018.03.019
Beer, J.S., John, O.P., Scabini, D., Knight, R.T., 2006. Orbitofrontal Cortex and Social Behavior: Integrating Self-monitoring and Emotion-Cognition Interactions. Journal of Cognitive Neuroscience 18, 871–879. https://doi.org/10.1162/jocn.2006.18.6.871
Belfry, K.D., Kolla, N.J., 2021. Cold-Blooded and on Purpose: A Review of the Biology of Proactive Aggression. Brain Sci 11, 1412. https://doi.org/10.3390/brainsci11111412
Benuzzi, F., Ballotta, D., Casadio, C., Zanelli, V., Porro, C.A., Nichelli, P.F., Lui, F., 2023. "When You're Smiling": How Posed Facial Expressions Affect Visual Recognition of Emotions. Brain Sci 13, 668. https://doi.org/10.3390/brainsci13040668
Beopoulos, A., Géa, M., Fasano, A., Iris, F., 2022. Autism spectrum disorders pathogenesis: Toward a comprehensive model based on neuroanatomic and neurodevelopment considerations. Front. Neurosci. 16. https://doi.org/10.3389/fnins.2022.988735
Berluti, K., Ploe, M.L., Marsh, A.A., 2023. Emotion processing in youths with conduct problems: an fMRI meta-analysis. Transl Psychiatry 13, 105. https://doi.org/10.1038/s41398-023-02363-z
Bernhardt, B.C., Singer, T., 2012. The Neural Basis of Empathy. Annu. Rev. Neurosci. 35, 1–23. https://doi.org/10.1146/annurev-neuro-062111-150536
Bershad, A.K., de Wit, H., 2025. Social Homeostasis and Psychoactive Drugs: What Can We Learn From Opioid and Amphetamine Drug Challenge

Studies in Humans? Biological Psychiatry, Social Homeostasis: A New Framework for Preventing and Treating Psychiatric Conditions 97, 982–988. https://doi.org/10.1016/j.biopsych.2024.09.006
Bertsch, K., Florange, J., Herpertz, S.C., 2020. Understanding Brain Mechanisms of Reactive Aggression. Curr Psychiatry Rep 22, 81. https://doi.org/10.1007/s11920-020-01208-6
Bhattacharjee, S., Kashyap, R., Abualait, T., Annabel Chen, S.-H., Yoo, W.-K., Bashir, S., 2021. The Role of Primary Motor Cortex: More Than Movement Execution. J Mot Behav 53, 258–274. https://doi.org/10.1080/00222895.2020.1738992
Bird, G., Viding, E., 2014. The self to other model of empathy: Providing a new framework for understanding empathy impairments in psychopathy, autism, and alexithymia. Neuroscience & Biobehavioral Reviews 47, 520–532. https://doi.org/10.1016/j.neubiorev.2014.09.021
Bishop, D.V.M., Maybery, M., Maley, A., Wong, D., Hill, W., Hallmayer, J., 2004. Using self-report to identify the broad phenotype in parents of children with autistic spectrum disorders: a study using the Autism-Spectrum Quotient. Journal of Child Psychology and Psychiatry 45, 1431–1436. https://doi.org/10.1111/j.1469-7610.2004.00325.x
Blair, J., White, S.F., 2013. Social cognition in individuals with psychopathic tendencies, in: Understanding Other Minds: Perspectives from Developmental Social Neuroscience, 3rd Ed. Oxford University Press, New York, NY, US, pp. 364–379. https://doi.org/10.1093/acprof:oso/9780199692972.003.0020
Blair, R.J., Colledge, E., Murray, L., Mitchell, D.G., 2001. A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. J Abnorm Child Psychol 29, 491–498. https://doi.org/10.1023/a:1012225108281
Blair, R.J.J., 2013. The neurobiology of psychopathic traits in youths. Nat Rev Neurosci 14, 786–799. https://doi.org/10.1038/nrn3577
Blair, R.J.R., 2008. Fine cuts of empathy and the amygdala: dissociable deficits in psychopathy and autism. Q J Exp Psychol (Hove) 61, 157–170. https://doi.org/10.1080/17470210701508855
Blair, R.J.R., 2005a. Responding to the emotions of others: Dissociating forms of empathy through the study of typical and psychiatric populations. Consciousness and Cognition, The Brain and Its Self 14, 698–718. https://doi.org/10.1016/j.concog.2005.06.004
Blair, R.J.R., 2005b. Applying a cognitive neuroscience perspective to the disorder of psychopathy. Development and Psychopathology 17, 865–891. https://doi.org/10.1017/S0954579405050418
Blair, R.J.R., Mitchell, D.G.V., Leonard, A., Budhani, S., Peschardt, K.S., Newman, C., 2004. Passive avoidance learning in individuals with psychopathy: modulation by reward but not by punishment. Personality and Individual Differences 37, 1179–1192. https://doi.org/10.1016/j.paid.2003.12.001
Blakemore, S.-J., 2012. Development of the social brain in adolescence. J R Soc Med 105, 111–116. https://doi.org/10.1258/jrsm.2011.110221
Blonigen, D.M., Hicks, B.M., Krueger, R.F., Patrick, C.J., Iacono, W.G., 2005. Psychopathic personality traits: heritability and genetic overlap with internalizing and externalizing psychopathology. Psychol Med 35, 637–648. https://doi.org/10.1017/S0033291704004180

Blum, K., Bowirrat, A., Sunder, K., Thanos, P.K., Hanna, C., Gold, M.S., Dennen, C.A., Elman, I., Murphy, K.T., Makale, M.T., 2024. Dopamine Dysregulation in Reward and Autism Spectrum Disorder. Brain Sciences 14, 733. https://doi.org/10.3390/brainsci14070733

Boedhoe, P.S.W., van Rooij, D., Hoogman, M., Twisk, J.W.R., Schmaal, L., Abe, Y., Alonso, P., Ameis, S.H., Anikin, A., Anticevic, A., Arango, C., Arnold, P.D., Asherson, P., Assogna, F., Auzias, G., Banaschewski, T., Baranov, A., Batistuzzo, M.C., Baumeister, S., Baur-Streubel, R., Behrmann, M., Bellgrove, M.A., Benedetti, F., Beucke, J.C., Biederman, J., Bollettini, I., Bose, A., Bralten, J., Bramati, I.E., Brandeis, D., Brem, S., Brennan, B.P., Busatto, G.F., Calderoni, S., Calvo, A., Calvo, R., Castellanos, F.X., Cercignani, M., Chaim-Avancini, T.M., Chantiluke, K.C., Cheng, Y., Cho, K.I.K., Christakou, A., Coghill, D., Conzelmann, A., Cubillo, A.I., Dale, A.M., Dallaspezia, S., Daly, E., Denys, D., Deruelle, C., Martino, A.D., Dinstein, I., Doyle, A.E., Durston, S., Earl, E.A., Ecker, C., Ehrlich, S., Ely, B.A., Epstein, J.N., Ethofer, T., Fair, D.A., Fallgatter, A.J., Faraone, S.V., Fedor, J., Feng, X., Feusner, J.D., Fitzgerald, J., Fitzgerald, K.D., Fouche, J.-P., Freitag, C.M., Fridgeirsson, E.A., Frodl, T., Gabel, M.C., Gallagher, L., Gogberashvili, T., Gori, I., Gruner, P., Gürsel, D.A., Haar, S., Haavik, J., Hall, G.B., Harrison, N.A., Hartman, C.A., Heslenfeld, D.J., Hirano, Y., Hoekstra, P.J., Hoexter, M.Q., Hohmann, S., Høvik, M.F., Hu, H., Huyser, C., Jahanshad, N., Jalbrzikowski, M., James, A., Janssen, J., Jaspers-Fayer, F., Jernigan, T.L., Kapilushniy, D., Kardatzki, B., Karkashadze, G., Kathmann, N., Kaufmann, C., Kelly, C., Khadka, S., King, J.A., Koch, K., Kohls, G., Kohls, K., Kuno, M., Kuntsi, J., Kvale, G., Kwon, J.S., Lázaro, L., Lera-Miguel, S., Lesch, K.-P., Hoekstra, L., Liu, Y., Lochner, C., Louza, M.R., Luna, B., Lundervold, A.J., Malpas, C.B., Marques, P., Marsh, R., Martínez-Zalacaín, I., Mataix-Cols, D., Mattos, P., McCarthy, H., McGrath, J., Mehta, M.A., Menchón, J.M., Mennes, M., Martinho, M.M., Moreira, P.S., Morer, A., Morgado, P., Muratori, F., Murphy, C.M., Murphy, D.G.M., Nakagawa, A., Nakamae, T., Nakao, T., Namazova-Baranova, L., Narayanaswamy, Janardhanan.C., Nicolau, R., Nigg, J.T., Novotny, S.E., Nurmi, E.L., Weiss, E.O., O'Gorman Tuura, R.L., O'Hearn, K., O'Neill, J., Oosterlaan, J., Oranje, B., Paloyelis, Y., Parellada, M., Pauli, P., Perriello, C., Piacentini, J., Piras, Fabrizio, Piras, Federica, Plessen, K.J., Puig, O., Ramos-Quiroga, J.A., Janardhan Reddy, Y.C., Reif, A., Reneman, L., Retico, A., Rosa, P.G.P., Rubia, K., Rus, O.G., Sakai, Y., Schrantee, A., Schwarz, L., Schweren, L.J.S., Seitz, J., Shaw, P., Shook, D., Silk, T.J., Simpson, H.B., Skokauskas, N., Soliva Vila, J.C., Solovieva, A., Soreni, N., Soriano-Mas, C., Spalletta, G., Stern, E.R., Stevens, M.C., Stewart, S.E., Sudre, G., Szeszko, P.R., Tamm, L., Taylor, M.J., Tolin, D.F., Tosetti, M., Tovar-Moll, F., Tsuchiyagaito, A., van Erp, T.G.M., van Wingen, G.A., Vance, A., Venkatasubramanian, G., Vilarroya, O., Vives-Gilabert, Y., von Polier, G.G., Walitza, S., Wallace, G.L., Wang, Z., Wolfers, T., Yoncheva, Y.N., Yun, J.-Y., Zanetti, M.V., Zhou, F., Ziegler, G.C., Zierhut, K.C., Zwiers, M.P., Thompson, P.M., Stein, D.J., Buitelaar, J., Franke, B., van den Heuvel, O.A., 2020. Subcortical brain volume, regional cortical thickness and cortical surface area across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD). Am J Psychiatry 177, 834–843. https://doi.org/10.1176/appi.ajp.2020.19030331

Bogdanova, O.V., Bogdanov, V.B., Pizano, A., Bouvard, M., Cazalets, J.-R., Mellen, N., Amestoy, A., 2022. The Current View on the Paradox of Pain in Autism Spectrum Disorders. Frontiers in Psychiatry 13.
Bonhomme, N., Esposito, E., 1998. Involvement of Serotonin and Dopamine in the Mechanism of Action of Novel Antidepressant Drugs: A Review. Journal of Clinical Psychopharmacology 18, 447.
Bons, D., van den Broek, E., Scheepers, F., Herpers, P., Rommelse, N., Buitelaaar, J.K., 2013. Motor, Emotional, and Cognitive Empathy in Children and Adolescents with Autism Spectrum Disorder and Conduct Disorder. J Abnorm Child Psychol 41, 425–443. https://doi.org/10.1007/s10802-012-9689-5
Book, A., Methot, T., Gauthier, N., Hosker-Field, A., Forth, A., Quinsey, V., Molnar, D., 2015. The Mask of Sanity Revisited: Psychopathic Traits and Affective Mimicry. Evolutionary Psychological Science 1, 91–102. https://doi.org/10.1007/s40806-015-0012-x
Braadbaart, L., De Grauw, H., Perrett, D.I., Waiter, G.D., Williams, J.H.G., 2014. The shared neural basis of empathy and facial imitation accuracy. NeuroImage 84, 367–375. https://doi.org/10.1016/j.neuroimage.2013.08.061
Braconnier, M.L., Siper, P.M., 2021. Neuropsychological Assessment in Autism Spectrum Disorder. Curr Psychiatry Rep 23, 63. https://doi.org/10.1007/s11920-021-01277-1
Braden, B.B., Riecken, C., 2019. Thinning faster? Age-related cortical thickness differences in adults with autism spectrum disorder. Research in Autism Spectrum Disorders 64, 31–38. https://doi.org/10.1016/j.rasd.2019.03.005
Brandl, F., Le Houcq Corbi, Z., Mulej Bratec, S., Sorg, C., 2019. Cognitive reward control recruits medial and lateral frontal cortices, which are also involved in cognitive emotion regulation: A coordinate-based meta-analysis of fMRI studies. NeuroImage 200, 659–673. https://doi.org/10.1016/j.neuroimage.2019.07.008
Brazil, K., 2016. Hare Psychopathy Checklist (PCL). https://doi.org/10.1007/978-3-319-28099-8_1079-1
Brinkley, C.A., Schmitt, W.A., Smith, S.S., Newman, J.P., 2001. Construct validation of a self-report psychopathy scale: does Levenson's self-report psychopathy scale measure the same constructs as Hare's psychopathy checklist-revised? Personality and Individual Differences 31, 1021–1038. https://doi.org/10.1016/S0191-8869(00)00178-1
Brugman, S., Cornet, L.J.M., Smeijers, D., Smeets, K., Oostermeijer, S., Buitelaar, J.K., Verkes, R.-J., Lobbestael, J., de Kogel, C.H., Jansen, L.M.C., 2017. Examining the reactive proactive questionnaire in adults in forensic and non-forensic settings: A variable- and person-based approach. Aggressive Behavior 43, 155–162. https://doi.org/10.1002/ab.21671
Buckholtz, J.W., Treadway, M.T., Cowan, R.L., Woodward, N.D., Benning, S.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Shelby, E.S., Smith, C.E., Cole, D., Kessler, R.M., Zald, D.H., 2010a. Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. Nat Neurosci 13, 419–421. https://doi.org/10.1038/nn.2510
Buckholtz, J.W., Treadway, M.T., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Shelby, E.S., Smith, C.E., Kessler, R.M., Zald, D.H., 2010b. Dopaminergic network differences in human impulsivity. Science 329, 532. https://doi.org/10.1126/science.1185778

Bulgarelli, C., Jones, E.J.H., 2023. The typical and atypical development of empathy: How big is the gap from lab to field? JCPP Advances 3, e12136. https://doi.org/10.1002/jcv2.12136
Burghart, M., Schmidt, S., Mier, D., 2024. Executive functions in psychopathy: a meta-analysis of inhibition, planning, shifting, and working memory performance. Psychological Medicine 54, 2823–2837. https://doi.org/10.1017/S0033291724001259
Bzdok, D., Langner, R., Schilbach, L., Engemann, D.A., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2013. Segregation of the human medial prefrontal cortex in social cognition. Front. Hum. Neurosci. 7. https://doi.org/10.3389/fnhum.2013.00232
Cacioppo, J.T., Hawkley, L.C., Norman, G.J., Berntson, G.G., 2011. Social isolation. Annals of the New York Academy of Sciences 1231, 17–22. https://doi.org/10.1111/j.1749-6632.2011.06028.x
Carlisi, C.O., Norman, L.J., Lukito, S.S., Radua, J., Mataix-Cols, D., Rubia, K., 2017. Comparative Multimodal Meta-analysis of Structural and Functional Brain Abnormalities in Autism Spectrum Disorder and Obsessive-Compulsive Disorder. Biol Psychiatry 82, 83–102. https://doi.org/10.1016/j.biopsych.2016.10.006
Carnevali, L., Valori, I., Mason, G., Altoè, G., Farroni, T., 2024. Interpersonal motor synchrony in autism: a systematic review and meta-analysis. Front. Psychiatry 15. https://doi.org/10.3389/fpsyt.2024.1355068
Carper, R.A., Courchesne, E., 2005. Localized enlargement of the frontal cortex in early autism. Biological Psychiatry 57, 126–133. https://doi.org/10.1016/j.biopsych.2004.11.005
Carr, L., Iacoboni, M., Dubeau, M.-C., Mazziotta, J.C., Lenzi, G.L., 2003. Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. Proceedings of the National Academy of Sciences 100, 5497–5502. https://doi.org/10.1073/pnas.0935845100
Carthy, E., Murphy, D., 2021. Comorbid Autism Spectrum Disorder and Antisocial Personality Disorder in Forensic Settings. The Journal of the American Academy of Psychiatry and the Law 49.
Caspers, S., Zilles, K., Laird, A.R., Eickhoff, S.B., 2010. ALE meta-analysis of action observation and imitation in the human brain. NeuroImage 50, 1148. https://doi.org/10.1016/j.neuroimage.2009.12.112
Chelnokova, O., Laeng, B., Eikemo, M., Riegels, J., Løseth, G., Maurud, H., Willoch, F., Leknes, S., 2014. Rewards of beauty: the opioid system mediates social motivation in humans. Mol Psychiatry 19, 746–747. https://doi.org/10.1038/mp.2014.1
Chen, C., Chen, Y.-H., Cheng, Y., 2022. Meta-analysis of functional neuroimaging and dispositional variables for clinical empathy. Neuroscience & Biobehavioral Reviews 142, 104874. https://doi.org/10.1016/j.neubiorev.2022.104874
Chevallier, C., Kohls, G., Troiani, V., Brodkin, E.S., Schultz, R.T., 2012. The Social Motivation Theory of Autism. Trends Cogn Sci 16, 231–239. https://doi.org/10.1016/j.tics.2012.02.007
Chuikova, Z.V., Filatov, A.A., Faber, A.Y., Arsalidou, M., 2025. Mapping common and distinct brain correlates among cognitive flexibility tasks: concordant evidence from meta-analyses. Brain Imaging and Behavior 19, 50–71. https://doi.org/10.1007/s11682-024-00921-7

Clark, T.F., Winkielman, P., McIntosh, D.N., 2008. Autism and the extraction of emotion from briefly presented facial expressions: stumbling at the first step of empathy. Emotion 8, 803–809. https://doi.org/10.1037/a0014124
Clements, C.C., Zoltowski, A.R., Yankowitz, L.D., Yerys, B.E., Schultz, R.T., Herrington, J.D., 2018. Evaluation of the Social Motivation Hypothesis of Autism: A Systematic Review and Meta-analysis. JAMA Psychiatry 75, 797. https://doi.org/10.1001/jamapsychiatry.2018.1100
Cohn, M.D., Pape, L.E., Schmaal, L., van den Brink, W., van Wingen, G., Vermeiren, R.R.J.M., Doreleijers, T.A.H., Veltman, D.J., Popma, A., 2015. Differential relations between juvenile psychopathic traits and resting state network connectivity. Human Brain Mapping 36, 2396–2405. https://doi.org/10.1002/hbm.22779
Colasanti, A., Searle, G.E., Long, C.J., Hill, S.P., Reiley, R.R., Quelch, D., Erritzoe, D., Tziortzi, A.C., Reed, L.J., Lingford-Hughes, A.R., Waldman, A.D., Schruers, K.R.J., Matthews, P.M., Gunn, R.N., Nutt, D.J., Rabiner, E.A., 2012. Endogenous Opioid Release in the Human Brain Reward System Induced by Acute Amphetamine Administration. Biological Psychiatry 72, 371–377. https://doi.org/10.1016/j.biopsych.2012.01.027
Collins, J., Horton, K., Gale-St. Ives, E., Murphy, G., Barnoux, M., 2023. A Systematic Review of Autistic People and the Criminal Justice System: An Update of King and Murphy (2014). Journal of Autism & Developmental Disorders 53, 3151–3179. https://doi.org/10.1007/s10803-022-05590-3
Cooke, D.J., Michie, C., 2001. Refining the construct of psychopathy: Towards a hierarchical model. Psychological Assessment 13, 171–188. https://doi.org/10.1037/1040-3590.13.2.171
Coplan, A., Goldie, P., 2011. EmpathyPhilosophical and Psychological Perspectives. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199539956.001.0001
Costello, H., Husain, M., Roiser, J.P., 2024. Apathy and Motivation: Biological Basis and Drug Treatment. Annu Rev Pharmacol Toxicol 64, 313–338. https://doi.org/10.1146/annurev-pharmtox-022423-014645
Courchesne, Eric, Campbell, K., Solso, S., 2011. Brain growth across the life span in autism: age-specific changes in anatomical pathology. Brain Res 1380, 138–145. https://doi.org/10.1016/j.brainres.2010.09.101
Courchesne, E., Karns, C., Davis, H., Ziccardi, R., Carper, R., Tigue, Z., Chisum, H.J., Moses, P., Pierce, K., Lord, C., Lincoln, A., Pizzo, S., Schreibman, L., Haas, R., Akshoomoff, N., Courchesne, R., 2011. Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. Neurology 76, 2111–2111. https://doi.org/10.1212/01.wnl.0000399191.79091.28
Courchesne, E., Karns, C.M., Davis, H.R., Ziccardi, R., Carper, R.A., Tigue, Z.D., Chisum, H.J., Moses, P., Pierce, K., Lord, C., Lincoln, A.J., Pizzo, S., Schreibman, L., Haas, R.H., Akshoomoff, N.A., Courchesne, R.Y., 2001. Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. Neurology 57, 245–254. https://doi.org/10.1212/WNL.57.2.245
Courchesne, E., Pierce, K., 2005. Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. International Journal of Developmental Neuroscience 23, 153–170. https://doi.org/10.1016/j.ijdevneu.2005.01.003

Courchesne, E., Pierce, K., Schumann, C.M., Redcay, E., Buckwalter, J.A., Kennedy, D.P., Morgan, J., 2007. Mapping Early Brain Development in Autism. Neuron 56, 399–413. https://doi.org/10.1016/j.neuron.2007.10.016
Cox, S.M.L., Frank, M.J., Larcher, K., Fellows, L.K., Clark, C.A., Leyton, M., Dagher, A., 2015. Striatal D1 and D2 signaling differentially predict learning from positive and negative outcomes. NeuroImage 109, 95–101. https://doi.org/10.1016/j.neuroimage.2014.12.070
Crego, C., Widiger, T.A., 2015. Psychopathy and the *DSM* . Journal of Personality 83, 665–677. https://doi.org/10.1111/jopy.12115
Cuff, B.M.P., Brown, S.J., Taylor, L., Howat, D.J., 2016. Empathy: A Review of the Concept. Emotion Review 8, 144–153. https://doi.org/10.1177/1754073914558466
Cúnico, S.D., Lermen, H.S., 2020. Prison from a gender perspective: a systematic review. Psicología, Conocimiento y Sociedad 10, 205–239.
da Cunha-Bang, S., Hjordt, L.V., Perfalk, E., Beliveau, V., Bock, C., Lehel, S., Thomsen, C., Sestoft, D., Svarer, C., Knudsen, G.M., 2017. Serotonin 1B Receptor Binding Is Associated With Trait Anger and Level of Psychopathy in Violent Offenders. Biological Psychiatry, Sociopathy, Impulsivity, Aggression 82, 267–274. https://doi.org/10.1016/j.biopsych.2016.02.030
Dadds, M.R., Cauchi, A.J., Wimalaweera, S., Hawes, D.J., Brennan, J., 2012. Outcomes, moderators, and mediators of empathic-emotion recognition training for complex conduct problems in childhood. Psychiatry Research 199, 201–207. https://doi.org/10.1016/j.psychres.2012.04.033
Dal Monte, O., Gangopadhyay, P., Putnam, P.T., Chang, S.W.C., 2025. Oxytocin and opioid antagonists: A dual approach to improving social behavior. Annals of the New York Academy of Sciences 1549, 55–71. https://doi.org/10.1111/nyas.15376
Dandil, Y., Smith, K., Kinnaird, E., Toloza, C., Tchanturia, K., 2020. Cognitive Remediation Interventions in Autism Spectrum Condition: A Systematic Review. Front. Psychiatry 11. https://doi.org/10.3389/fpsyt.2020.00722
Davis, M.H., 2011. Interpersonal Reactivity Index. https://doi.org/10.1037/t01093-000
De Brito, S., Frick, P., copeland, william, odgers, candice, Franke, B., Freitag, C., Hawes, D., Watson, P., Fairchild, G., 2019. Fairchild et al. (2019) Conduct disorder primer.
De Brito, S.A., Forth, A.E., Baskin-Sommers, A.R., Brazil, I.A., Kimonis, E.R., Pardini, D., Frick, P.J., Blair, R.J.R., Viding, E., 2021a. Psychopathy. Nat Rev Dis Primers 7, 49. https://doi.org/10.1038/s41572-021-00282-1
De Brito, S.A., McDonald, D., Camilleri, J.A., Rogers, J.C., 2021b. Cortical and subcortical gray matter volume in psychopathy: A voxel-wise meta-analysis. Journal of Abnormal Psychology 130, 627–640. https://doi.org/10.1037/abn0000698
Deb, S., Roy, M., Limbu, B., Brizard, B.A., Murugan, M., Roy, A., Santambrogio, J., 2023. Randomised controlled trials of antipsychotics for people with autism spectrum disorder: a systematic review and a meta-analysis. Psychological Medicine 53, 7964–7972. https://doi.org/10.1017/S003329172300212X
Deisinger, J.A., 2011. Chapter 10 History of autism spectrum disorders, in: Rotatori, A.F., Obiakor, F.E., Bakken, J.P. (Eds.), History of Special

Education. Emerald Group Publishing Limited, p. 0. https://doi.org/10.1108/S0270-4013(2011)0000021013
DeJesus, B.M., Oliveira, R.C., De Carvalho, F.O., De Jesus Mari, J., Arida, R.M., Teixeira-Machado, L., 2020. Dance promotes positive benefits for negative symptoms in autism spectrum disorder (ASD): A systematic review. Complementary Therapies in Medicine 49, 102299. https://doi.org/10.1016/j.ctim.2020.102299
Del Pozzo, J., Roché, M.W., Silverstein, S.M., 2018. Violent behavior in autism spectrum disorders: Who's at risk? Aggression and Violent Behavior 39, 53–60. https://doi.org/10.1016/j.avb.2018.01.007
Delobel-Ayoub, M., Saemundsen, E., Gissler, M., Ego, A., Moilanen, I., Ebeling, H., Rafnsson, V., Klapouszczak, D., Thorsteinsson, E., Arnaldsdóttir, K.M., Roge, B., Arnaud, C., Schendel, D., 2020. Prevalence of Autism Spectrum Disorder in 7–9-Year-Old Children in Denmark, Finland, France and Iceland: A Population-Based Registries Approach Within the ASDEU Project. J Autism Dev Disord 50, 949–959. https://doi.org/10.1007/s10803-019-04328-y
Demetriou, E.A., Lampit, A., Quintana, D.S., Naismith, S.L., Song, Y.J.C., Pye, J.E., Hickie, I., Guastella, A.J., 2018. Autism spectrum disorders: a meta-analysis of executive function. Mol Psychiatry 23, 1198–1204. https://doi.org/10.1038/mp.2017.75
Deming, P., Koenigs, M., 2020. Functional neural correlates of psychopathy: a meta-analysis of MRI data. Transl Psychiatry 10, 133. https://doi.org/10.1038/s41398-020-0816-8
Dempsey, E.E., Moore, C., Johnson, S.A., Stewart, S.H., Smith, I.M., 2020. Morality in autism spectrum disorder: A systematic review. Development and Psychopathology 32, 1069–1085. https://doi.org/10.1017/S0954579419001160
Di Giovanni, G., Esposito, E., Di Matteo, V., 2010. Role of Serotonin in Central Dopamine Dysfunction. CNS Neuroscience & Therapeutics 16, 179–194. https://doi.org/10.1111/j.1755-5949.2010.00135.x
Di Martino, A., Ross, K., Uddin, L.Q., Sklar, A.B., Castellanos, F.X., Milham, M.P., 2009. Functional Brain Correlates of Social and Non-Social Processes in Autism Spectrum Disorders: an ALE Meta-Analysis. Biol Psychiatry 65, 63–74. https://doi.org/10.1016/j.biopsych.2008.09.022
Di, X., Azeez, A., Li, X., Haque, E., Biswal, B.B., 2018. Disrupted focal white matter integrity in autism spectrum disorder: a voxel-based meta-analysis of diffusion tensor imaging studies. Prog Neuropsychopharmacol Biol Psychiatry 82, 242–248. https://doi.org/10.1016/j.pnpbp.2017.11.007
Diamond, A., 2013. Executive Functions. Annu. Rev. Psychol. 64, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750
Dichter, G.S., Felder, J.N., Green, S.R., Rittenberg, A.M., Sasson, N.J., Bodfish, J.W., 2012. Reward circuitry function in autism spectrum disorders. Soc Cogn Affect Neurosci 7, 160–172. https://doi.org/10.1093/scan/nsq095
Dickstein, D.P., Pescosolido, M.F., Reidy, B.L., Galvan, T., Kim, K.L., Seymour, K.E., Laird, A.R., Di Martino, A., Barrett, R.P., 2013. Developmental Meta-Analysis of the Functional Neural Correlates of Autism Spectrum Disorders. J Am Acad Child Adolesc Psychiatry 52, 279-289.e16. https://doi.org/10.1016/j.jaac.2012.12.012

Dimberg, U., Thunberg, M., 1998. Rapid facial reactions to emotional facial expressions. Scand J Psychol 39, 39–45. https://doi.org/10.1111/1467-9450.00054
Downing, P.E., Jiang, Y., Shuman, M., Kanwisher, N., 2001. A Cortical Area Selective for Visual Processing of the Human Body. Science 293, 2470–2473. https://doi.org/10.1126/science.1063414
Drevets, W.C., Gautier, C., Price, J.C., Kupfer, D.J., Kinahan, P.E., Grace, A.A., Price, J.L., Mathis, C.A., 2001. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. Biological Psychiatry 49, 81–96. https://doi.org/10.1016/S0006-3223(00)01038-6
Dubol, M., Trichard, C., Leroy, C., Sandu, A.-L., Rahim, M., Granger, B., Tzavara, E.T., Karila, L., Martinot, J.-L., Artiges, E., 2018. Dopamine Transporter and Reward Anticipation in a Dimensional Perspective: A Multimodal Brain Imaging Study. Neuropsychopharmacol. 43, 820–827. https://doi.org/10.1038/npp.2017.183
Duerler, P., Vollenweider, F.X., Preller, K.H., 2022. A neurobiological perspective on social influence: Serotonin and social adaptation. Journal of Neurochemistry 162, 60–79. https://doi.org/10.1111/jnc.15607
Dugré, J.R., De Brito, S.A., 2025. Mapping the psychopathic brain: Divergent neuroimaging findings converge onto a common brain network. Neuroscience & Biobehavioral Reviews 176, 106272. https://doi.org/10.1016/j.neubiorev.2025.106272
Dugré, J.R., Potvin, S., 2021. Impaired attentional and socio-affective networks in subjects with antisocial behaviors: a meta-analysis of resting-state functional connectivity studies. Psychological Medicine 51, 1249–1259. https://doi.org/10.1017/S0033291721001525
Dugré, J.R., Radua, J., Carignan-Allard, M., Dumais, A., Rubia, K., Potvin, S., 2020. Neurofunctional abnormalities in antisocial spectrum: A meta-analysis of fMRI studies on Five distinct neurocognitive research domains. Neuroscience & Biobehavioral Reviews 119, 168–183. https://doi.org/10.1016/j.neubiorev.2020.09.013
Durand, G., Rutten, B.P.F., Lobbestael, J., 2023. Exploring the Relationship Between Cognitive Abilities and Adaptive Components of Psychopathic Traits. Sage Open 13, 21582440231173823. https://doi.org/10.1177/21582440231173823
Ecker, C., Spooren, W., Murphy, D.G.M., 2013. Translational approaches to the biology of Autism: false dawn or a new era? Mol Psychiatry 18, 435–442. https://doi.org/10.1038/mp.2012.102
Edwards, L.A., 2014. A Meta-Analysis of Imitation Abilities in Individuals With Autism Spectrum Disorders. Autism Research 7, 363–380. https://doi.org/10.1002/aur.1379
Eidenmueller, K., Grimm, F., Hermann, D., Frischknecht, U., Montag, C., Dziobek, I., Kiefer, F., Bekier, N.K., 2021. Exploring Influences on Theory of Mind Impairment in Opioid Dependent Patients. Frontiers in Psychiatry 12.
Eigsti, I.-M., 2013. A Review of Embodiment in Autism Spectrum Disorders. Front. Psychol. 4. https://doi.org/10.3389/fpsyg.2013.00224
Eisenberger, N.I., 2012. The neural bases of social pain: Evidence for shared representations with physical pain. Psychosom Med 74, 126–135. https://doi.org/10.1097/PSY.0b013e3182464dd1

Elsabbagh, M., Divan, G., Koh, Y.-J., Kim, Y.S., Kauchali, S., Marcín, C., Montiel-Nava, C., Patel, V., Paula, C.S., Wang, C., Yasamy, M.T., Fombonne, E., 2012. Global Prevalence of Autism and Other Pervasive Developmental Disorders. Autism Res 5, 160–179. https://doi.org/10.1002/aur.239

Eres, R., Louis, W.R., Molenberghs, P., 2018. Common and distinct neural networks involved in fMRI studies investigating morality: an ALE meta-analysis. Social Neuroscience 13, 384–398. https://doi.org/10.1080/17470919.2017.1357657

Ernst, M., Zametkin, A.J., Matochik, J.A., Pascualvaca, D., Cohen, R.M., 1997. Low medial prefrontal dopaminergic activity in autistic children. Lancet 350, 638. https://doi.org/10.1016/s0140-6736(05)63326-0

Escobar, A. del P., Casanova, J.P., Andrés, M.E., Fuentealba, J.A., 2020. Crosstalk Between Kappa Opioid and Dopamine Systems in Compulsive Behaviors. Frontiers in Pharmacology 11.

Esler, A.N., Bal, V.H., Guthrie, W., Wetherby, A., Weismer, S.E., Lord, C., 2015. The Autism Diagnostic Observation Schedule, Toddler Module: Standardized Severity Scores. J Autism Dev Disord 45, 2704–2720. https://doi.org/10.1007/s10803-015-2432-7

Espinoza, F.A., Anderson, N.E., Vergara, V.M., Harenski, C.L., Decety, J., Rachakonda, S., Damaraju, E., Koenigs, M., Kosson, D.S., Harenski, K., Calhoun, V.D., Kiehl, K.A., 2019. Resting-state fMRI dynamic functional network connectivity and associations with psychopathy traits. NeuroImage: Clinical 24, 101970. https://doi.org/10.1016/j.nicl.2019.101970

Fallon, N., Roberts, C., Stancak, A., 2020. Shared and distinct functional networks for empathy and pain processing: a systematic review and meta-analysis of fMRI studies. Social Cognitive and Affective Neuroscience 15, 709–723. https://doi.org/10.1093/scan/nsaa090

Fan, Y., Duncan, N.W., de Greck, M., Northoff, G., 2011. Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. Neurosci Biobehav Rev 35, 903–911. https://doi.org/10.1016/j.neubiorev.2010.10.009

Fathabadipour, S., Mohammadi, Z., Roshani, F., Goharbakhsh, N., Alizadeh, H., Palizgar, F., Cumming, P., Michel, T.M., Vafaee, M.S., 2022. The neural effects of oxytocin administration in autism spectrum disorders studied by fMRI: A systematic review. Journal of Psychiatric Research 154, 80–90. https://doi.org/10.1016/j.jpsychires.2022.06.033

Fazio, R.L., Pietz, C.A., Denney, R.L., 2012. An Estimate of the Prevalence of Autism-Spectrum Disorders in an Incarcerated Population 4.

Feltes, P.K., De Boer, S.F., 2021. Mapping and Imaging the Aggressive Brain in Animals and Humans, in: Dierckx, R.A.J.O., Otte, A., De Vries, E.F.J., Van Waarde, A., Sommer, I.E. (Eds.), PET and SPECT in Psychiatry. Springer International Publishing, Cham, pp. 887–926. https://doi.org/10.1007/978-3-030-57231-0_28

Ferguson, A.M., Cameron, C.D., Inzlicht, M., 2020. Motivational effects on empathic choices. Journal of Experimental Social Psychology 90, 104010. https://doi.org/10.1016/j.jesp.2020.104010

Fernandes, J.M., Cajão, R., Lopes, R., Jerónimo, R., Barahona-Corrêa, J.B., 2018. Social Cognition in Schizophrenia and Autism Spectrum Disorders: A Systematic Review and Meta-Analysis of Direct Comparisons. Front. Psychiatry 9. https://doi.org/10.3389/fpsyt.2018.00504

Fernández, M., Mollinedo-Gajate, I., Peñagarikano, O., 2018. Neural Circuits for Social Cognition: Implications for Autism. Neuroscience 370, 148–162. https://doi.org/10.1016/j.neuroscience.2017.07.013
Fernell, E., Watanabe, Y., Adolfsson, I., Tani, Y., Bergström, M., Hartvig, P., Lilja, A., von Knorring, A.L., Gillberg, C., Långström, B., 1997. Possible effects of tetrahydrobiopterin treatment in six children with autism--clinical and positron emission tomography data: a pilot study. Dev Med Child Neurol 39, 313–318. https://doi.org/10.1111/j.1469-8749.1997.tb07437.x
Fields, H.L., Margolis, E.B., 2015. Understanding opioid reward. Trends Neurosci 38, 217–225. https://doi.org/10.1016/j.tins.2015.01.002
Fitzgerald, M., 2019. Empathy: Autism and Psychopathy. Empathy Study. https://doi.org/10.5772/intechopen.82886
Fitzpatrick, S.E., Srivorakiat, L., Wink, L.K., Pedapati, E.V., Erickson, C.A., 2016. Aggression in autism spectrum disorder: presentation and treatment options. NDT 12, 1525–1538. https://doi.org/10.2147/NDT.S84585
Florea, T., Palimariciuc, M., Cristofor, A.C., Dobrin, I., Chiriță, R., Bîrsan, M., Dobrin, R.P., Pădurariu, M., 2022. Oxytocin: Narrative Expert Review of Current Perspectives on the Relationship with Other Neurotransmitters and the Impact on the Main Psychiatric Disorders. Medicina 58, 923. https://doi.org/10.3390/medicina58070923
Fordham, A.-J., Hacherl, C.-C., Patel, N., Jones, K., Myers, B., Abraham, M., Gendreau, J., 2021. Differentiating Glioblastomas from Solitary Brain Metastases: An Update on the Current Literature of Advanced Imaging Modalities. Cancers 13, 2960. https://doi.org/10.3390/cancers13122960
Foulkes, L., McCrory, E.J., Neumann, C.S., Viding, E., 2014a. Inverted Social Reward: Associations between Psychopathic Traits and Self-Report and Experimental Measures of Social Reward. PLOS ONE 9, e106000. https://doi.org/10.1371/journal.pone.0106000
Foulkes, L., Seara-Cardoso, A., Neumann, C.S., Rogers, J.S.C., Viding, E., 2014b. Looking After Number One: Associations Between Psychopathic Traits and Measures of Social Motivation and Functioning in a Community Sample of Males. J Psychopathol Behav Assess 36, 22–29. https://doi.org/10.1007/s10862-013-9381-2
Fournier, K.A., Hass, C.J., Naik, S.K., Lodha, N., Cauraugh, J.H., 2010. Motor Coordination in Autism Spectrum Disorders: A Synthesis and Meta-Analysis. J Autism Dev Disord 40, 1227–1240. https://doi.org/10.1007/s10803-010-0981-3
Franz, M., Nordmann, M.A., Rehagel, C., Schäfer, R., Müller, T., Lundqvist, D., 2021. It is in your face-Alexithymia impairs facial mimicry. Emotion 21, 1537–1549. https://doi.org/10.1037/emo0001002
Frazier, A., Ferreira, P.A., Gonzales, J.E., 2019. Born this way? A review of neurobiological and environmental evidence for the etiology of psychopathy. Personality Neuroscience 2, e8. https://doi.org/10.1017/pen.2019.7
Frühholz, S., Grandjean, D., 2013. Multiple subregions in superior temporal cortex are differentially sensitive to vocal expressions: A quantitative meta-analysis. Neuroscience & Biobehavioral Reviews 37, 24–35. https://doi.org/10.1016/j.neubiorev.2012.11.002
Fuccillo, M.V., 2016. Striatal Circuits as a Common Node for Autism Pathophysiology. Frontiers in Neuroscience 10.

Fung, L.K., Mahajan, R., Nozzolillo, A., Bernal, P., Krasner, A., Jo, B., Coury, D., Whitaker, A., Veenstra-Vanderweele, J., Hardan, A.Y., 2016. Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. Pediatrics 137, S124–S135. https://doi.org/10.1542/peds.2015-2851K

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., Perez, J., McGuire, P., Politi, P., 2009. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 34, 418–432. https://doi.org/10.1139/jpn.0953

Gallese, V., 2007. The Shared Manifold Hypothesis: embodied simulation and its role in empathy and social cognition, in: Farrow, T.F.D., Woodruff, P.W.R. (Eds.), Empathy in Mental Illness. Cambridge University Press, pp. 448–472. https://doi.org/10.1017/CBO9780511543753.025

Gallese, V., 2003. The Roots of Empathy: The Shared Manifold Hypothesis and the Neural Basis of Intersubjectivity. Psychopathology 36, 171–180. https://doi.org/10.1159/000072786

Gandolphe, M.-C., Lecluyse, B., Triquet, C., Brunelle, E., Duparcq, J.-P., Nandrino, J.-L., 2018. Mind reading abilities in opiate-dependent patients: An exploratory study. Comprehensive Psychiatry 83, 46–52. https://doi.org/10.1016/j.comppsych.2018.03.001

Gao, S., Wang, X., Su, Y., 2023. Examining whether adults with autism spectrum disorder encounter multiple problems in theory of mind: a study based on meta-analysis. Psychon Bull Rev 30, 1740–1758. https://doi.org/10.3758/s13423-023-02280-8

Gao, Y., Glenn, A.L., Schug, R.A., Yang, Y., Raine, A., 2009. The Neurobiology of Psychopathy: A Neurodevelopmental Perspective. Can J Psychiatry 54, 813–823. https://doi.org/10.1177/070674370905401204

Glenn, A.L., Raine, A., 2008. The Neurobiology of Psychopathy. Psychiatric Clinics of North America, Recent Research in Personality Disorders 31, 463–475. https://doi.org/10.1016/j.psc.2008.03.004

Glenn, A.L., Yang, Y., 2012. The Potential Role of the Striatum in Antisocial Behavior and Psychopathy. Biological Psychiatry, Substance Abuse and Psychosis 72, 817–822. https://doi.org/10.1016/j.biopsych.2012.04.027

Glerean, E., Pan, R.K., Salmi, J., Kujala, R., Lahnakoski, J.M., Roine, U., Nummenmaa, L., Leppämäki, S., Nieminen-von Wendt, T., Tani, P., Saramäki, J., Sams, M., Jääskeläinen, I.P., 2016. Reorganization of functionally connected brain subnetworks in high-functioning autism. Human Brain Mapping 37, 1066–1079. https://doi.org/10.1002/hbm.23084

Goodwill, A.M., Low, L.T., Fox, P.T., Fox, P.M., Poon, K.K., Bhowmick, S.S., Chen, S.H.A., 2023. Meta-analytic connectivity modelling of functional magnetic resonance imaging studies in autism spectrum disorders. Brain Imaging Behav 17, 257–269. https://doi.org/10.1007/s11682-022-00754-2

Gossen, A., Groppe, S.E., Winkler, L., Kohls, G., Herrington, J., Schultz, R.T., Gründer, G., Spreckelmeyer, K.N., 2014. Neural evidence for an association between social proficiency and sensitivity to social reward. Social Cognitive and Affective Neuroscience 9, 661–670. https://doi.org/10.1093/scan/nst033

Grace, A.A., Floresco, S.B., Goto, Y., Lodge, D.J., 2007. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends in Neurosciences 30, 220–227. https://doi.org/10.1016/j.tins.2007.03.003
Greaves-Lord, K., Skuse, D., Mandy, W., 2022. Innovations of the ICD-11 in the Field of Autism Spectrum Disorder: A Psychological Approach. Clin Psychol Eur 4, e10005. https://doi.org/10.32872/cpe.10005
Green, M.F., Horan, W.P., Lee, J., 2015. Social cognition in schizophrenia. Nat Rev Neurosci 16, 620–631. https://doi.org/10.1038/nrn4005
Grosbras, M.-H., Beaton, S., Eickhoff, S.B., 2012. Brain regions involved in human movement perception: A quantitative voxel-based meta-analysis. Human Brain Mapping 33, 431–454. https://doi.org/10.1002/hbm.21222
Guo, Z., Tang, X., Xiao, S., Yan, H., Sun, S., Yang, Z., Huang, L., Chen, Z., Wang, Y., 2024. Systematic review and meta-analysis: multimodal functional and anatomical neural alterations in autism spectrum disorder. Mol Autism 15, 16. https://doi.org/10.1186/s13229-024-00593-6
Gur, R.C., 2005. Brain maturation and its relevance to understanding criminal culpability of juveniles. Curr Psychiatry Rep 7, 292–296. https://doi.org/10.1007/s11920-005-0083-7
H. Roder, C., Marie Hoogendam, J., M. van der Veen, F., 2010. FMRI, Antipsychotics and Schizophrenia. Influence of Different Antipsychotics on BOLD-Signal. Current Pharmaceutical Design 16, 2012–2025. https://doi.org/10.2174/138161210791293088
Hagelberg, N., Martikainen, I.K., Mansikka, H., Hinkka, S., Någren, K., Hietala, J., Scheinin, H., Pertovaara, A., 2002. Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity. PAIN 99, 273. https://doi.org/10.1016/S0304-3959(02)00121-5
Hamilton, R.K.B., Hiatt Racer, K., Newman, J.P., 2015. Impaired integration in psychopathy: A unified theory of psychopathic dysfunction. Psychological Review 122, 770–791. https://doi.org/10.1037/a0039703
Han, M., Jiang, G., Luo, H., Shao, Y., 2021. Neurobiological Bases of Social Networks. Front. Psychol. 12. https://doi.org/10.3389/fpsyg.2021.626337
Hare, R.D., 2011. Psychopathy Checklist—Revised. https://doi.org/10.1037/t01167-000
Harms, M.B., Martin, A., Wallace, G.L., 2010. Facial emotion recognition in autism spectrum disorders: a review of behavioral and neuroimaging studies. Neuropsychol Rev 20, 290–322. https://doi.org/10.1007/s11065-010-9138-6
Harmsen, I.E., 2019. Empathy in Autism Spectrum Disorder. Journal of Autism & Developmental Disorders 49, 3939–3955. https://doi.org/10.1007/s10803-019-04087-w
Harris, H.N., Peng, Y.B., 2020. Evidence and explanation for the involvement of the nucleus accumbens in pain processing. Neural Regeneration Research 15, 597. https://doi.org/10.4103/1673-5374.266909
Hastings, M.E., Tangney, J.P., Stuewig, J., 2008. Psychopathy and identification of facial expressions of emotion. Personality and Individual Differences 44, 1474–1483. https://doi.org/10.1016/j.paid.2008.01.004
Hatfield, E., Cacioppo, J.T., Rapson, R.L., 1993. Emotional Contagion. Curr Dir Psychol Sci 2, 96–100. https://doi.org/10.1111/1467-8721.ep10770953
Hecht, L.K., Latzman, R.D., 2018. Exploring the differential associations between components of executive functioning and reactive and proactive aggression.

Journal of Clinical and Experimental Neuropsychology 40, 62–74. https://doi.org/10.1080/13803395.2017.1314450
Heiss, W.-D., Herholz, K., 2006. Brain receptor imaging. J Nucl Med 47, 302–312.
Helt, M.S., Sorensen, T.M., Scheub, R.J., Nakhle, M.B., Luddy, A.C., 2021. Patterns of Contagious Yawning and Itching Differ Amongst Adults With Autistic Traits vs. Psychopathic Traits. Front. Psychol. 12. https://doi.org/10.3389/fpsyg.2021.645310
Henry, J.D., Von Hippel, W., Molenberghs, P., Lee, T., Sachdev, P.S., 2016. Clinical assessment of social cognitive function in neurological disorders. Nat Rev Neurol 12, 28–39. https://doi.org/10.1038/nrneurol.2015.229
Herpers, P.C.M., Scheepers, F.E., Bons, D.M.A., Buitelaar, J.K., Rommelse, N.N.J., 2014. The cognitive and neural correlates of psychopathy and especially callous–unemotional traits in youths: A systematic review of the evidence. Development and Psychopathology 26, 245–273. https://doi.org/10.1017/S0954579413000527
Hill, A.P., Zuckerman, K.E., Hagen, A.D., Kriz, D.J., Duvall, S.W., van Santen, J., Nigg, J., Fair, D., Fombonne, E., 2014. Aggressive behavior problems in children with autism spectrum disorders: Prevalence and correlates in a large clinical sample. Research in Autism Spectrum Disorders 8, 1121–1133. https://doi.org/10.1016/j.rasd.2014.05.006
Hippler, K., Viding, E., Klicpera, C., Happé, F., 2010. Brief Report: No Increase in Criminal Convictions in Hans Asperger's Original Cohort. J Autism Dev Disord 40, 774–780. https://doi.org/10.1007/s10803-009-0917-y
Hirota, T., King, B.H., 2023. Autism Spectrum Disorder: A Review. JAMA 329, 157. https://doi.org/10.1001/jama.2022.23661
Hirvonen, J., Aalto, S., Hagelberg, N., Maksimow, A., Ingman, K., Oikonen, V., Virkkala, J., Någren, K., Scheinin, H., 2009. Measurement of central μ-opioid receptor binding in vivo with PET and [11C]carfentanil: a test-retest study in healthy subjects. European Journal of Nuclear Medicine and Molecular Imaging 36, 275–286.
Hirvonen, J., Aalto, S., Lumme, V., Någren, K., Kajander, J., Vilkman, H., Hagelberg, N., Oikonen, V., Hietala, J., 2003. Measurement of striatal and thalamic dopamine D2 receptor binding with 11C-raclopride. Nuclear Medicine Communications 24, 1207.
Hogeveen, J., Salvi, C., Grafman, J., 2016. 'Emotional Intelligence': Lessons from Lesions. Trends Neurosci 39, 694–705. https://doi.org/10.1016/j.tins.2016.08.007
Holland, A.C., O'Connell, G., Dziobek, I., 2021. Facial mimicry, empathy, and emotion recognition: a meta-analysis of correlations. Cognition and Emotion 35, 150–168. https://doi.org/10.1080/02699931.2020.1815655
Horley, J., 2014. The emergence and development of psychopathy. History of the Human Sciences 27, 91–110. https://doi.org/10.1177/0952695114541864
Hostetler, C.M., Hinde, K., Maninger, N., Mendoza, S.P., Mason, W.A., Rowland, D.J., Wang, G.B., Kukis, D., Cherry, S.R., Bales, K.L., 2017. Effects of pair bonding on dopamine D1 receptors in monogamous male titi monkeys (Callicebus cupreus). Am J Primatol 79, 1–9. https://doi.org/10.1002/ajp.22612
Hsu, C.-T., Neufeld, J., Chakrabarti, B., 2018a. Reduced reward-related neural response to mimicry in individuals with autism. European Journal of Neuroscience 47, 610–618. https://doi.org/10.1111/ejn.13620

Hsu, C.-T., Sims, T., Chakrabarti, B., 2018b. How mimicry influences the neural correlates of reward: An fMRI study. Neuropsychologia 116, 61–67. https://doi.org/10.1016/j.neuropsychologia.2017.08.018
Hsu, D.T., Sanford, B.J., Meyers, K.K., Love, T.M., Hazlett, K.E., Wang, H., Ni, L., Walker, S.J., Mickey, B.J., Korycinski, S.T., Koeppe, R.A., Crocker, J.K., Langenecker, S.A., Zubieta, J.-K., 2013. Response of the μ-opioid system to social rejection and acceptance. Mol Psychiatry 18, 1211–1217. https://doi.org/10.1038/mp.2013.96
Huang, Y., Huang, X., Ebstein, R.P., Yu, R., 2021. Intranasal oxytocin in the treatment of autism spectrum disorders: A multilevel meta-analysis. Neuroscience & Biobehavioral Reviews 122, 18–27. https://doi.org/10.1016/j.neubiorev.2020.12.028
Huettel, S.A., Song, A.W., McCarthy, G., 2004. Functional magnetic resonance imaging. Sinauer Associates, Sunderland, Mass.
Huey, E.D., Putnam, K.T., Grafman, J., 2006. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. Neurology 66, 17–22. https://doi.org/10.1212/01.wnl.0000191304.55196.4d
Hulka, L.M., Eisenegger, C., Preller, K.H., Vonmoos, M., Jenni, D., Bendrick, K., Baumgartner, M.R., Seifritz, E., Quednow, B.B., 2014. Altered social and non-social decision-making in recreational and dependent cocaine users. Psychol. Med. 44, 1015–1028. https://doi.org/10.1017/S0033291713001839
Hung, Y., Gaillard, S.L., Yarmak, P., Arsalidou, M., 2018. Dissociations of cognitive inhibition, response inhibition, and emotional interference: Voxelwise ALE meta-analyses of fMRI studies. Human Brain Mapping 39, 4065–4082. https://doi.org/10.1002/hbm.24232
Iacoboni, M., 2009. Imitation, Empathy, and Mirror Neurons. Annual Review of Psychology 60, 653–670. https://doi.org/10.1146/annurev.psych.60.110707.163604
Ilioska, I., Oldehinkel, M., Llera, A., Chopra, S., Looden, T., Chauvin, R., Van Rooij, D., Floris, D.L., Tillmann, J., Moessnang, C., Banaschewski, T., Holt, R.J., Loth, E., Charman, T., Murphy, D.G.M., Ecker, C., Mennes, M., Beckmann, C.F., Fornito, A., Buitelaar, J.K., 2023. Connectome-wide Mega-analysis Reveals Robust Patterns of Atypical Functional Connectivity in Autism. Biol Psychiatry 94, 29–39. https://doi.org/10.1016/j.biopsych.2022.12.018
Im, D.S., 2016. Template to Perpetrate: An Update on Violence in Autism Spectrum Disorder. Harv Rev Psychiatry 24, 14–35. https://doi.org/10.1097/HRP.0000000000000087
Inagaki, T.K., Hazlett, L.I., Andreescu, C., 2020. Opioids and social bonding: Effect of naltrexone on feelings of social connection and ventral striatum activity to close others. Journal of Experimental Psychology: General 149, 732–745. https://doi.org/10.1037/xge0000674
Ingersoll, B., Berger, N., Carlsen, D., Hamlin, T., 2017. Improving social functioning and challenging behaviors in adolescents with ASD and significant ID: A randomized pilot feasibility trial of reciprocal imitation training in a residential setting. Developmental Neurorehabilitation 20, 236–246. https://doi.org/10.1080/17518423.2016.1211187
Innis, R.B., Cunningham, V.J., Delforge, J., Fujita, M., Gjedde, A., Gunn, R.N., Holden, J., Houle, S., Huang, S.-C., Ichise, M., Iida, H., Ito, H., Kimura, Y.,

Koeppe, R.A., Knudsen, G.M., Knuuti, J., Lammertsma, A.A., Laruelle, M., Logan, J., Maguire, R.P., Mintun, M.A., Morris, E.D., Parsey, R., Price, J.C., Slifstein, M., Sossi, V., Suhara, T., Votaw, J.R., Wong, D.F., Carson, R.E., 2007. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27, 1533–1539. https://doi.org/10.1038/sj.jcbfm.9600493

Isen, J.D., Baker, L.A., L. Kern, M., Raine, A., Bezdjian, S., 2018. Unmasking the association between psychopathic traits and adaptive functioning in children. Personality and Individual Differences 124, 57–65. https://doi.org/10.1016/j.paid.2017.11.043

Jambroes, T., Jansen, L.M.C., v.d. Ven, P.M., Claassen, T., Glennon, J.C., Vermeiren, R.R.J.M., Doreleijers, T.A.H., Popma, A., 2018. Dimensions of psychopathy in relation to proactive and reactive aggression: Does intelligence matter? Personality and Individual Differences 129, 76–82. https://doi.org/10.1016/j.paid.2018.03.001

Janouschek, H., Chase, H.W., Sharkey, R.J., Peterson, Z.J., Camilleri, J.A., Abel, T., Eickhoff, S.B., Nickl-Jockschat, T., 2021. The functional neural architecture of dysfunctional reward processing in autism. NeuroImage: Clinical 31, 102700. https://doi.org/10.1016/j.nicl.2021.102700

Jantzi, C., Moulin, V., 2025. The new ICD-11 diagnosis of personality disorder in forensic psychiatry. Front. Psychiatry 16. https://doi.org/10.3389/fpsyt.2025.1630512

Jauhar, S., Fortea, L., Solanes, A., Albajes-Eizagirre, A., McKenna, P.J., Radua, J., 2021. Brain activations associated with anticipation and delivery of monetary reward: A systematic review and meta-analysis of fMRI studies. PLoS One 16, e0255292. https://doi.org/10.1371/journal.pone.0255292

Jeandarme, I., Goktas, G., Boucké, J., Dekkers, I., De Boel, L., Verbeke, G., 2022. High Security Settings in Flanders: An Analysis of Discharged and Long-Term Forensic Psychiatric Patients. Front. Psychiatry 13. https://doi.org/10.3389/fpsyt.2022.826406

Johanson, M., Vaurio, O., Tiihonen, J., Lähteenvuo, M., 2020. A Systematic Literature Review of Neuroimaging of Psychopathic Traits. Front. Psychiatry 10. https://doi.org/10.3389/fpsyt.2019.01027

Jones, A.P., Happé, F.G.E., Gilbert, F., Burnett, S., Viding, E., 2010. Feeling, caring, knowing: different types of empathy deficit in boys with psychopathic tendencies and autism spectrum disorder. J Child Psychol Psychiatry 51, 1188–1197. https://doi.org/10.1111/j.1469-7610.2010.02280.x

Jones, A.P., Larsson, H., Ronald, A., Rijsdijk, F., Busfield, P., Mcmillan, A., Plomin, R., Viding, E., 2009. Phenotypic and Aetiological Associations Between Psychopathic Tendencies, Autistic Traits, and Emotion Attribution. Criminal Justice and Behavior 36, 1198–1212. https://doi.org/10.1177/0093854809342949

Jones-Tabah, J., Mohammad, H., Paulus, E.G., Clarke, P.B.S., Hébert, T.E., 2022. The Signaling and Pharmacology of the Dopamine D1 Receptor. Front. Cell. Neurosci. 15. https://doi.org/10.3389/fncel.2021.806618

Junewicz, A., Billick, S.B., 2020. Conduct Disorder: Biology and Developmental Trajectories. Psychiatr Q 91, 77–90. https://doi.org/10.1007/s11126-019-09678-5

Jüriloo, A., Lauerma, H., Holmalahti, T., Tyni, S., Aarnio, J., Viitanen, P., Wuolijoki, T., Mattila, A., Lintonen, T., Joukamaa, M., Vartiainen, H.,

2014. Psychopathic traits in a representative sample of Finnish male prisoners. Nordic Journal of Psychiatry 68, 117–122. https://doi.org/10.3109/08039488.2013.780259
Kanne, S.M., Mazurek, M.O., 2011. Aggression in Children and Adolescents with ASD: Prevalence and Risk Factors. Journal of Autism & Developmental Disorders 41, 926–937. https://doi.org/10.1007/s10803-010-1118-4
Kanthan, M., Cumming, P., Hooker, J.M., Vasdev, N., 2017. Classics in Neuroimaging: Imaging the Dopaminergic Pathway with PET. ACS Chem. Neurosci. 8, 1817–1819. https://doi.org/10.1021/acschemneuro.7b00252
Karjalainen, T., Karlsson, H.K., Lahnakoski, J.M., Glerean, E., Nuutila, P., Jääskeläinen, I.P., Hari, R., Sams, M., Nummenmaa, L., 2017. Dissociable Roles of Cerebral μ-Opioid and Type 2 Dopamine Receptors in Vicarious Pain: A Combined PET–fMRI Study. Cereb Cortex 27, 4257–4266. https://doi.org/10.1093/cercor/bhx129
Karjalainen, T., Tuisku, J., Santavirta, S., Kantonen, T., Bucci, M., Tuominen, L., Hirvonen, J., Hietala, J., Rinne, J.O., Nummenmaa, L., 2020. Magia: Robust Automated Image Processing and Kinetic Modeling Toolbox for PET Neuroinformatics. Frontiers in Neuroinformatics 14.
Karjalainen, T., Tuominen, L., Manninen, S., Kalliokoski, K.K., Nuutila, P., Jääskeläinen, I.P., Hari, R., Sams, M., Nummenmaa, L., 2016. Behavioural activation system sensitivity is associated with cerebral μ-opioid receptor availability. Soc Cogn Affect Neurosci 11, 1310–1316. https://doi.org/10.1093/scan/nsw044
Kaur, T., Wiesner, N., Kilbourn, M.R., Scott, P.J.H., 2020. Classics in Neuroimaging: Shedding Light on Opioid Receptors with Positron Emission Tomography Imaging. ACS Chem. Neurosci. 11, 2906–2914. https://doi.org/10.1021/acschemneuro.0c00593
Keech, B., Crowe, S., Hocking, D.R., 2018. Intranasal oxytocin, social cognition and neurodevelopmental disorders: A meta-analysis. Psychoneuroendocrinology 87, 9–19. https://doi.org/10.1016/j.psyneuen.2017.09.022
Kelsey, K.R., Rogers, R., Robinson, E.V., 2015. Self-Report Measures of Psychopathy: What is their Role in Forensic Assessments? J Psychopathol Behav Assess 37, 380–391. https://doi.org/10.1007/s10862-014-9475-5
Keysers, C., Kaas, J.H., Gazzola, V., 2010. Somatosensation in social perception. Nat Rev Neurosci 11, 417–428. https://doi.org/10.1038/nrn2833
Kheiri, F., Bragin, A., Engel, J., 2013. Functional Connectivity between Brain Areas Estimated by Analysis of Gamma Waves. J Neurosci Methods 214, 184–191. https://doi.org/10.1016/j.jneumeth.2013.01.007
Khvatskaya, Y., Lenzenweger, M.F., 2016. Motor Empathy in Individuals With Psychopathic Traits: A Preliminary Study. Journal of Personality Disorders 30, 613–632. https://doi.org/10.1521/pedi_2015_29_219
Kiehl, K.A., 2006. A cognitive neuroscience perspective on psychopathy: Evidence for paralimbic system dysfunction. Psychiatry Research 142, 107–128. https://doi.org/10.1016/j.psychres.2005.09.013
Kim, J.-H., Son, Y.-D., Kim, H.-K., Lee, S.-Y., Kim, Y.-B., Cho, Z.-H., 2014. Dopamine D2/3 receptor availability and human cognitive impulsivity: a high-resolution positron emission tomography imaging study with [11C]raclopride. Acta Neuropsychiatrica 26, 35–42. https://doi.org/10.1017/neu.2013.29

Kimonis, E.R., Fleming, G., Briggs, N., Brouwer-French, L., Frick, P.J., Hawes, D.J., Bagner, D.M., Thomas, R., Dadds, M., 2019. Parent-Child Interaction Therapy Adapted for Preschoolers with Callous-Unemotional Traits: An Open Trial Pilot Study. Journal of Clinical Child & Adolescent Psychology 48, S347–S361. https://doi.org/10.1080/15374416.2018.1479966
King, C., Murphy, G.H., 2014. A Systematic Review of People with Autism Spectrum Disorder and the Criminal Justice System. J Autism Dev Disord 44, 2717–2733. https://doi.org/10.1007/s10803-014-2046-5
Kirsch, H.E., 2006. Social cognition and epilepsy surgery. Epilepsy & Behavior 8, 71–80. https://doi.org/10.1016/j.yebeh.2005.09.002
Kirst, S., Bögl, K., Gross, V.L., Diehm, R., Poustka, L., Dziobek, I., 2022. Subtypes of Aggressive Behavior in Children with Autism in the Context of Emotion Recognition, Hostile Attribution Bias, and Dysfunctional Emotion Regulation. Journal of Autism & Developmental Disorders 52, 5367–5382. https://doi.org/10.1007/s10803-021-05387-w
Klapwijk, E.T., Aghajani, M., Colins, O.F., Marijnissen, G.M., Popma, A., van Lang, N.D.J., van der Wee, N.J.A., Vermeiren, R.R.J.M., 2016. Different brain responses during empathy in autism spectrum disorders versus conduct disorder and callous-unemotional traits. J Child Psychol Psychiatry 57, 737–747. https://doi.org/10.1111/jcpp.12498
Kohls, G., Chevallier, C., Troiani, V., Schultz, R., 2012. Social "wanting" dysfunction in autism: Neurobiological underpinnings and treatment implications. Journal of neurodevelopmental disorders 4, 10. https://doi.org/10.1186/1866-1955-4-10
Kohn, N., Eickhoff, S.B., Scheller, M., Laird, A.R., Fox, P.T., Habel, U., 2014. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. Neuroimage 87, 345–355. https://doi.org/10.1016/j.neuroimage.2013.11.001
Kolla, N.J., Houle, S., 2019. Single-Photon Emission Computed Tomography and Positron Emission Tomography Studies of Antisocial Personality Disorder and Aggression: a Targeted Review. Curr Psychiatry Rep 21, 24. https://doi.org/10.1007/s11920-019-1011-6
Korkmaz, B., 2011. Theory of Mind and Neurodevelopmental Disorders of Childhood. Pediatr Res 69, 101–108. https://doi.org/10.1203/PDR.0b013e318212c177
Koshiyama, D., Fukunaga, M., Okada, N., Morita, K., Nemoto, K., Usui, K., Yamamori, H., Yasuda, Y., Fujimoto, M., Kudo, N., Azechi, H., Watanabe, Y., Hashimoto, N., Narita, H., Kusumi, I., Ohi, K., Shimada, T., Kataoka, Y., Yamamoto, M., Ozaki, N., Okada, G., Okamoto, Y., Harada, K., Matsuo, K., Yamasue, H., Abe, O., Hashimoto, Ryuichiro, Takahashi, T., Hori, T., Nakataki, M., Onitsuka, T., Holleran, L., Jahanshad, N., Van Erp, T.G.M., Turner, J., Donohoe, G., Thompson, P.M., Kasai, K., Hashimoto, Ryota, COCORO, 2020. White matter microstructural alterations across four major psychiatric disorders: mega-analysis study in 2937 individuals. Mol Psychiatry 25, 883–895. https://doi.org/10.1038/s41380-019-0553-7
Kosillo, P., Bateup, H.S., 2021. Dopaminergic Dysregulation in Syndromic Autism Spectrum Disorders: Insights From Genetic Mouse Models. Frontiers in Neural Circuits 15.
Kowalewska, B., Drozdz, W., Kowalewski, L., 2022. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) in

autism research: literature review. Ir J Psychol Med 39, 272–286. https://doi.org/10.1017/ipm.2021.15
Krakowski, M., 2003. Violence and Serotonin: Influence of Impulse Control, Affect Regulation, and Social Functioning. JNP 15, 294–305. https://doi.org/10.1176/jnp.15.3.294
Krupicz, M., 2014. Critical review: the efficacy of Reciprocal Imitation Training as a treatment for imitation deficits in young children with Autism Spectrum Disorder. School of Communication Sciences and Disorders.
Krysko, K.M., Rutherford, M.D., 2009. A threat-detection advantage in those with autism spectrum disorders. Brain and Cognition 69, 472–480. https://doi.org/10.1016/j.bandc.2008.10.002
Kubota, M., Fujino, J., Tei, S., Takahata, K., Matsuoka, K., Tagai, K., Sano, Y., Yamamoto, Y., Shimada, H., Takado, Y., Seki, C., Itahashi, T., Aoki, Y.Y., Ohta, H., Hashimoto, R., Zhang, M.-R., Suhara, T., Nakamura, M., Takahashi, H., Kato, N., Higuchi, M., 2020. Binding of Dopamine D1 Receptor and Noradrenaline Transporter in Individuals with Autism Spectrum Disorder: A PET Study. Cerebral Cortex 30, 6458–6468. https://doi.org/10.1093/cercor/bhaa211
Künecke, J., Mokros, A., Olderbak, S., Wilhelm, O., 2018. Facial responsiveness of psychopaths to the emotional expressions of others. PLOS ONE 13, e0190714. https://doi.org/10.1371/journal.pone.0190714
Kyranides, M.N., Lu, K.M., Ten Seldam, S., 2024. Differences in emotional contagion, interpersonal relationships and social rewards in males and females: examining the links with primary and secondary psychopathic traits. Curr Psychol 43, 300–315. https://doi.org/10.1007/s12144-023-04236-6
Kyranides, M.N., Petridou, M., Gokani, H.A., Hill, S., Fanti, K.A., 2023. Reading and reacting to faces, the effect of facial mimicry in improving facial emotion recognition in individuals with antisocial behavior and psychopathic traits. Curr Psychol 42, 14306–14319. https://doi.org/10.1007/s12144-022-02749-0
Kyte, D., Jerram, M., DiBiase, R., 2020. Brain opioid theory of social attachment: A review of evidence for approach motivation to harm. Motivation Science 6, 12–20. https://doi.org/10.1037/mot0000135
Labarca, P., Cristian, O., González-Loyola, M., Wenceslao, P., 2025. Effective Interventions in the Treatment of Self-Harming Behavior in Children and Adolescents with Autism Spectrum Disorder: A Review. Children 12, 1184–1200. https://doi.org/10.3390/children12091184
Lai, M.-C., Lombardo, M.V., Auyeung, B., Chakrabarti, B., Baron-Cohen, S., 2015. Sex/Gender Differences and Autism: Setting the Scene for Future Research. Journal of the American Academy of Child & Adolescent Psychiatry 54, 11–24. https://doi.org/10.1016/j.jaac.2014.10.003
Lam, K.S.L., Aman, M.G., Arnold, L.E., 2006. Neurochemical correlates of autistic disorder: A review of the literature. Research in Developmental Disabilities 27, 254–289. https://doi.org/10.1016/j.ridd.2005.03.003
Lammertsma, A.A., Hume, S.P., 1996. Simplified Reference Tissue Model for PET Receptor Studies. NeuroImage 4, 153–158. https://doi.org/10.1006/nimg.1996.0066
Langen, M., Durston, S., Kas, M.J.H., Van Engeland, H., Staal, W.G., 2011a. The neurobiology of repetitive behavior: …and men. Neuroscience &

Biobehavioral Reviews 35, 356–365. https://doi.org/10.1016/j.neubiorev.2010.02.005
Langen, M., Kas, M.J.H., Staal, W.G., van Engeland, H., Durston, S., 2011b. The neurobiology of repetitive behavior: Of mice…. Neuroscience & Biobehavioral Reviews 35, 345–355. https://doi.org/10.1016/j.neubiorev.2010.02.004
Larsson, H., Andershed, H., Lichtenstein, P., 2006. A genetic factor explains most of the variation in the psychopathic personality. Journal of Abnormal Psychology 115, 221–230. https://doi.org/10.1037/0021-843X.115.2.221
Laruelle, M., 2000a. Imaging Synaptic Neurotransmission with in Vivo Binding Competition Techniques: A Critical Review. J Cereb Blood Flow Metab 20, 423–451. https://doi.org/10.1097/00004647-200003000-00001
Laruelle, M., 2000b. The role of model-based methods in the development of single scan techniques. Nuclear Medicine and Biology 27, 637–642. https://doi.org/10.1016/S0969-8051(00)00142-6
Lau, W.K.W., Leung, M.-K., Lau, B.W.M., 2019. Resting-state abnormalities in Autism Spectrum Disorders: A meta-analysis. Sci Rep 9, 3892. https://doi.org/10.1038/s41598-019-40427-7
Lau, W.K.W., Leung, M.-K., Zhang, R., 2020. Hypofunctional connectivity between the posterior cingulate cortex and ventromedial prefrontal cortex in autism: Evidence from coordinate-based imaging meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 103, 109986. https://doi.org/10.1016/j.pnpbp.2020.109986
Leigh, R., Oishi, K., Hsu, J., Lindquist, M., Gottesman, R.F., Jarso, S., Crainiceanu, C., Mori, S., Hillis, A.E., 2013. Acute lesions that impair affective empathy. Brain 136, 2539–2549. https://doi.org/10.1093/brain/awt177
Leising, D., Grande, T., Faber, R., 2009. The Toronto Alexithymia Scale (TAS-20): A measure of general psychological distress. Journal of Research in Personality 43, 707–710. https://doi.org/10.1016/j.jrp.2009.03.009
Lenzen, L.M., Donges, M.R., Eickhoff, S.B., Poeppl, T.B., 2021. Exploring the Neural Correlates of (Altered) Moral Cognition in Psychopaths. Behav. Sci. & L. 39, 731–740.
Levenson, M., Kiehl, K., Fitzpatrick, C., 1995. Assessing Psychopathic Attributes in a Noninstitutionalized Population. Journal of personality and social psychology 68, 151–8. https://doi.org/10.1037//0022-3514.68.1.151
Li, X., Zhang, K., He, X., Zhou, J., Jin, C., Shen, L., Gao, Y., Tian, M., Zhang, H., 2021. Structural, Functional, and Molecular Imaging of Autism Spectrum Disorder. Neurosci Bull 37, 1051–1071. https://doi.org/10.1007/s12264-021-00673-0
Ligneul, R., Mainen, Z.F., 2023. Serotonin. Current Biology 33, R1216–R1221. https://doi.org/10.1016/j.cub.2023.09.068
Liloia, D., Manuello, J., Costa, T., Keller, R., Nani, A., Cauda, F., 2024. Atypical local brain connectivity in pediatric autism spectrum disorder? A coordinate-based meta-analysis of regional homogeneity studies. Eur Arch Psychiatry Clin Neurosci 274, 3–18. https://doi.org/10.1007/s00406-022-01541-2
Liu, J., Yao, L., Zhang, W., Xiao, Y., Liu, L., Gao, X., Shah, C., Li, S., Tao, B., Gong, Q., Lui, S., 2017. Gray matter abnormalities in pediatric autism spectrum disorder: a meta-analysis with signed differential mapping. Eur Child

Adolesc Psychiatry 26, 933–945. https://doi.org/10.1007/s00787-017-0964-4
Liu, M., Liu, C.H., Zheng, S., Zhao, K., Fu, X., 2021. Reexamining the neural network involved in perception of facial expression: A meta-analysis. Neuroscience & Biobehavioral Reviews 131, 179–191. https://doi.org/10.1016/j.neubiorev.2021.09.024
Liu, X., Eickhoff, S.B., Caspers, S., Wu, J., Genon, S., Hoffstaedter, F., Mars, R.B., Sommer, I.E., Eickhoff, C.R., Chen, J., Jardri, R., Reetz, K., Dogan, I., Aleman, A., Kogler, L., Gruber, O., Caspers, J., Mathys, C., Patil, K.R., 2021. Functional parcellation of human and macaque striatum reveals human-specific connectivity in the dorsal caudate. NeuroImage 235, 118006. https://doi.org/10.1016/j.neuroimage.2021.118006
Liu, X., Hairston, J., Schrier, M., Fan, J., 2011. Common and distinct networks underlying reward valence and processing stages: A meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev 35, 1219–1236. https://doi.org/10.1016/j.neubiorev.2010.12.012
Lockwood, P.L., Bird, G., Bridge, M., Viding, E., 2013. Dissecting empathy: high levels of psychopathic and autistic traits are characterized by difficulties in different social information processing domains. Front. Hum. Neurosci. 7. https://doi.org/10.3389/fnhum.2013.00760
Lord, C., Brugha, T.S., Charman, T., Cusack, J., Dumas, G., Frazier, T., Jones, E.J.H., Jones, R.M., Pickles, A., State, M.W., Taylor, J.L., Veenstra-VanderWeele, J., 2020. Autism spectrum disorder. Nat Rev Dis Primers 6, 5. https://doi.org/10.1038/s41572-019-0138-4
Lord, C., Charman, T., Havdahl, A., Carbone, P., Anagnostou, E., Boyd, B., Carr, T., de Vries, P.J., Dissanayake, C., Divan, G., Freitag, C.M., Gotelli, M.M., Kasari, C., Knapp, M., Mundy, P., Plank, A., Scahill, L., Servili, C., Shattuck, P., Simonoff, E., Singer, A.T., Slonims, V., Wang, P.P., Ysrraelit, M.C., Jellett, R., Pickles, A., Cusack, J., Howlin, P., Szatmari, P., Holbrook, A., Toolan, C., McCauley, J.B., 2022. The *Lancet* Commission on the future of care and clinical research in autism. The Lancet 399, 271–334. https://doi.org/10.1016/S0140-6736(21)01541-5
Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., Schopler, E., 1989. Austism diagnostic observation schedule: A standardized observation of communicative and social behavior. J Autism Dev Disord 19, 185–212. https://doi.org/10.1007/BF02211841
Lord, C., Rutter, M., Le Couteur, A., 1994. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24, 659–685. https://doi.org/10.1007/BF02172145
Løseth, G., Trøstheim, M., Leknes, S., 2024. Endogenous mu-opioid modulation of social connection in humans: a systematic review and meta-analysis. Transl Psychiatry 14, 379. https://doi.org/10.1038/s41398-024-03088-3
Loseth, G.E., Ellingsen, D.-M., Leknes, S., 2014. State-dependent µ-opioid Modulation of Social Motivation – a model. Front. Behav. Neurosci. 8. https://doi.org/10.3389/fnbeh.2014.00430
Loureiro, D., Machado, A., Silva, T., Veigas, T., Ramalheira, C., Cerejeira, J., 2018. Higher Autistic Traits Among Criminals, But No Link to Psychopathy: Findings from a High-Security Prison in Portugal. Journal of Autism & Developmental Disorders 48, 3010–3020. https://doi.org/10.1007/s10803-018-3576-z

Love, T.M., Stohler, C.S., Zubieta, J.-K., 2009. PET Measures of Endogenous Opioid Neurotransmission Predict Impulsiveness Traits in Humans. Arch Gen Psychiatry 66, 1124–1134. https://doi.org/10.1001/archgenpsychiatry.2009.134
Luckhurst, C., Hatfield, E., Gelvin-Smith, C., 2017. Capacity for Empathy and Emotional Contagion in Those With Psychopathic Personalities. Interpersona: An International Journal on Personal Relationships 11, 70–91. https://doi.org/10.5964/ijpr.v11i1.247
Lukito, S., Norman, L., Carlisi, C., Radua, J., Hart, H., Simonoff, E., Rubia, K., 2020. Comparative meta-analyses of brain structural and functional abnormalities during cognitive control in attention-deficit/hyperactivity disorder and autism spectrum disorder. Psychol Med 50, 894–919. https://doi.org/10.1017/S0033291720000574
Lukkarinen, L., Tuisku, J., Sun, L., Helin, S., Karlsson, H.K., Venetjoki, N., Salomaa, M., Rautio, P., Hirvonen, J., Lauerma, H., Tiihonen, J., Nummenmaa, L., 2024. Aberrant type 2 dopamine receptor availability in violent offenders with psychopathy. Neuroimage 297, 120724. https://doi.org/10.1016/j.neuroimage.2024.120724
Lydon, S., Healy, O., O'Callaghan, O., Mulhern, T., Holloway, J., 2015. A Systematic Review of the Treatment of Fears and Phobias Among Children with Autism Spectrum Disorders. Rev J Autism Dev Disord 2, 141–154. https://doi.org/10.1007/s40489-014-0043-4
MacDonald, G., Leary, M.R., 2005. Why Does Social Exclusion Hurt? The Relationship Between Social and Physical Pain. Psychological Bulletin 131, 202–223. https://doi.org/10.1037/0033-2909.131.2.202
MacDonald, K., MacDonald, T.M., 2010. The Peptide That Binds: A Systematic Review of Oxytocin and its Prosocial Effects in Humans. Harvard Review of Psychiatry 18, 1–21. https://doi.org/10.3109/10673220903523615
Machin, A.J., Dunbar, R.I.M., 2011. The brain opioid theory of social attachment: a review of the evidence. Behaviour 148, 985–1025.
Magno, M.A., Canu, E., Filippi, M., Agosta, F., 2022. Social cognition in the FTLD spectrum: evidence from MRI. J Neurol 269, 2245–2258. https://doi.org/10.1007/s00415-021-10892-0
Maguire, K., Warman, H., Blumenfeld, F., Langdon, P.E., 2024. The relationship between psychopathy and autism: a systematic review and narrative synthesis. Front. Psychiatry 15. https://doi.org/10.3389/fpsyt.2024.1375170
Majuri, J., Joutsa, J., Arponen, E., Forsback, S., Kaasinen, V., 2018. Dopamine synthesis capacity correlates with μ-opioid receptor availability in the human basal ganglia: A triple-tracer PET study. NeuroImage 183, 1–6. https://doi.org/10.1016/j.neuroimage.2018.07.069
Malén, T., Karjalainen, T., Isojärvi, J., Vehtari, A., Bürkner, P.-C., Putkinen, V., Kaasinen, V., Hietala, J., Nuutila, P., Rinne, J., Nummenmaa, L., 2022. Atlas of type 2 dopamine receptors in the human brain: Age and sex dependent variability in a large PET cohort. NeuroImage 255, 119149. https://doi.org/10.1016/j.neuroimage.2022.119149
Malén, T., Santavirta, S., De Maeyer, S., Tuisku, J., Kaasinen, V., Kankare, T., Isojärvi, J., Rinne, J., Hietala, J., Nuutila, P., Nummenmaa, L., 2024. Alterations in type 2 dopamine receptors across neuropsychiatric conditions: A large-scale PET cohort. NeuroImage: Clinical 41, 103578. https://doi.org/10.1016/j.nicl.2024.103578

Mandic-Maravic, V., Grujicic, R., Milutinovic, L., Munjiza-Jovanovic, A., Pejovic-Milovancevic, M., 2022. Dopamine in Autism Spectrum Disorders—Focus on D2/D3 Partial Agonists and Their Possible Use in Treatment. Frontiers in Psychiatry 12.

Manninen, S., Tuominen, L., Dunbar, R.I., Karjalainen, T., Hirvonen, J., Arponen, E., Hari, R., Jääskeläinen, I.P., Sams, M., Nummenmaa, L., 2017. Social Laughter Triggers Endogenous Opioid Release in Humans. J. Neurosci. 37, 6125–6131. https://doi.org/10.1523/JNEUROSCI.0688-16.2017

Maoz, H., Tsviban, L., Gvirts, H.Z., Shamay-Tsoory, S.G., Levkovitz, Y., Watemberg, N., Bloch, Y., 2014. Stimulants improve theory of mind in children with attention deficit/hyperactivity disorder. J Psychopharmacol 28, 212–219. https://doi.org/10.1177/0269881113492030

Margolis, E.B., Hjelmstad, G.O., Fujita, W., Fields, H.L., 2014. Direct Bidirectional μ-Opioid Control of Midbrain Dopamine Neurons. J Neurosci 34, 14707–14716. https://doi.org/10.1523/JNEUROSCI.2144-14.2014

Marotta, R., Risoleo, M.C., Messina, G., Parisi, L., Carotenuto, M., Vetri, L., Roccella, M., 2020. The Neurochemistry of Autism. Brain Sci 10, 163. https://doi.org/10.3390/brainsci10030163

Mars, R.B., Neubert, F.-X., Noonan, M.P., Sallet, J., Toni, I., Rushworth, M.F.S., 2012. On the relationship between the "default mode network" and the "social brain." Front. Hum. Neurosci. 6. https://doi.org/10.3389/fnhum.2012.00189

Marsh, A.A., Blair, R.J.R., 2008. Deficits in facial affect recognition among antisocial populations: a meta-analysis. Neurosci Biobehav Rev 32, 454–465. https://doi.org/10.1016/j.neubiorev.2007.08.003

Marshall, J., Watts, A.L., Lilienfeld, S.O., 2018. Do psychopathic individuals possess a misaligned moral compass? A meta-analytic examination of psychopathy's relations with moral judgment. Personality Disorders: Theory, Research, and Treatment 9, 40–50. https://doi.org/10.1037/per0000226

Martín-Rodríguez, J.F., León-Carrión, J., 2010. Theory of mind deficits in patients with acquired brain injury: A quantitative review. Neuropsychologia 48, 1181–1191. https://doi.org/10.1016/j.neuropsychologia.2010.02.009

Massaccesi, C., Korb, S., Götzendorfer, S., Chiappini, E., Willeit, M., Lundström, J.N., Windischberger, C., Eisenegger, C., Silani, G., 2024. Effects of dopamine and opioid receptor antagonism on the neural processing of social and nonsocial rewards. Human Brain Mapping 45, e26645. https://doi.org/10.1002/hbm.26645

Mattavelli, G., Gorrino, I., Tornaghi, D., Canessa, N., 2024. Cognitive and motor impulsivity in the healthy brain, and implications for eating disorders and obesity: A coordinate-based meta-analysis and systematic review. Cortex 171, 90–112. https://doi.org/10.1016/j.cortex.2023.10.008

Mauchand, M., Zhang, S., 2023. Disentangling emotional signals in the brain: an ALE meta-analysis of vocal affect perception. Cognitive, Affective & Behavioral Neuroscience 23, 17–29. https://doi.org/10.3758/s13415-022-01030-y

May, K.E., Kana, R.K., 2020. Frontoparietal Network in Executive Functioning in Autism Spectrum Disorder. Autism Research 13, 1762–1777. https://doi.org/10.1002/aur.2403

McCall, C., Singer, T., 2012. The animal and human neuroendocrinology of social cognition, motivation and behavior. Nat Neurosci 15, 681–688. https://doi.org/10.1038/nn.3084
McClintock, K., Hall, S., Oliver, C., 2003. Risk markers associated with challenging behaviours in people with intellectual disabilities: a meta-analytic study. Journal of Intellectual Disability Research 47, 405–416. https://doi.org/10.1046/j.1365-2788.2003.00517.x
McCrory, E.J., n.d. Genetic and neurocognitive contributions to the development of psychopathy.
McDonald, S., Darke, S., Kaye, S., Torok, M., 2013. Deficits in social perception in opioid maintenance patients, abstinent opioid users and non-opioid users. Addiction 108, 566–574. https://doi.org/10.1111/add.12040
McIntosh, D.N., Reichmann-Decker, A., Winkielman, P., Wilbarger, J.L., 2006. When the social mirror breaks: deficits in automatic, but not voluntary, mimicry of emotional facial expressions in autism. Developmental Science 9, 295–302. https://doi.org/10.1111/j.1467-7687.2006.00492.x
Meffert, H., Gazzola, V., den Boer, J.A., Bartels, A.A.J., Keysers, C., 2013. Reduced spontaneous but relatively normal deliberate vicarious representations in psychopathy. Brain 136, 2550–2562. https://doi.org/10.1093/brain/awt190
Meloy, J.R., 2025. Affective and predatory violence: from evolutionary adaptation to psychiatric morbidity. Front. Psychiatry 16. https://doi.org/10.3389/fpsyt.2025.1690508
Mende-Siedlecki, P., Said, C.P., Todorov, A., 2013. The social evaluation of faces: a meta-analysis of functional neuroimaging studies. Soc Cogn Affect Neurosci 8, 285–299. https://doi.org/10.1093/scan/nsr090
Meyer-Lindenberg, A., Buckholtz, J.W., Kolachana, B., R. Hariri, A., Pezawas, L., Blasi, G., Wabnitz, A., Honea, R., Verchinski, B., Callicott, J.H., Egan, M., Mattay, V., Weinberger, D.R., 2006. Neural mechanisms of genetic risk for impulsivity and violence in humans. Proceedings of the National Academy of Sciences 103, 6269–6274. https://doi.org/10.1073/pnas.0511311103
Meza, N., Rees, R., Escobar Liquitay, C.M., Franco, J.V., Sguassero, Y., Williams, K., Pringsheim, T., Rojas, V., Madrid, E., 2022. Atypical antipsychotics for autism spectrum disorder: a network meta-analysis. Cochrane Database of Systematic Reviews 2022. https://doi.org/10.1002/14651858.CD014965
Michels, M., 2021. General Intelligence and the Dark Triad. Journal of Individual Differences.
Mick, I., Myers, J., Stokes, P.R.A., Erritzoe, D., Colasanti, A., Bowden-Jones, H., Clark, L., Gunn, R.N., Rabiner, E.A., Searle, G.E., Waldman, A.D., Parkin, M.C., Brailsford, A.D., Nutt, D.J., Lingford-Hughes, A.R., 2014. Amphetamine induced endogenous opioid release in the human brain detected with [11C]carfentanil PET: replication in an independent cohort. Int. J. Neuropsychopharm. 17, 2069–2074. https://doi.org/10.1017/S1461145714000704
Mier, D., Haddad, L., Diers, K., Dressing, H., Meyer-Lindenberg, A., Kirsch, P., 2014. Reduced embodied simulation in psychopathy. World Journal of Biological Psychiatry 15, 479–487. https://doi.org/10.3109/15622975.2014.902541
Mintun, M.A., Raichle, M.E., Kilbourn, M.R., Wooten, G.F., Welch, M.J., 1984. A quantitative model for the in vivo assessment of drug binding sites with

positron emission tomography. Annals of Neurology 15, 217–227. https://doi.org/10.1002/ana.410150302
Mohr, P., Masopust, J., Kopeček, M., 2022. Dopamine Receptor Partial Agonists: Do They Differ in Their Clinical Efficacy? Front. Psychiatry 12. https://doi.org/10.3389/fpsyt.2021.781946
Molenberghs, P., Johnson, H., Henry, J.D., Mattingley, J.B., 2016. Understanding the minds of others: A neuroimaging meta-analysis. Neuroscience & Biobehavioral Reviews 65, 276–291. https://doi.org/10.1016/j.neubiorev.2016.03.020
Morrissey, C., Hollin, C., 2011. Antisocial and Psychopathic Personality Disorders in Forensic Intellectual Disability Populations: What Do We Know So Far? Forensic Research in Offenders with Intellectual & Developmental Disabilities Part 2: Review Paper. Psych., Crime & L. 17, 133–150.
Mosconi, M., Zwaigenbaum, L., Piven, J., 2006. Structural MRI in autism: Findings and future directions. Clinical Neuroscience Research, Recent Advances in Autism and Related Disorders 6, 135–144. https://doi.org/10.1016/j.cnr.2006.06.010
Mosconi, M.W., Sweeney, J.A., 2015. Sensorimotor dysfunctions as primary features of autism spectrum disorders 8.
Mostofsky, S.H., Burgess, M.P., Gidley Larson, J.C., 2007. Increased motor cortex white matter volume predicts motor impairment in autism. Brain 130, 2117–2122. https://doi.org/10.1093/brain/awm129
Moul, C., Killcross, S., Dadds, M.R., 2012. A model of differential amygdala activation in psychopathy. Psychological Review 119, 789–806. https://doi.org/10.1037/a0029342
Murayama, C., Iwabuchi, T., Kato, Y., Yokokura, M., Harada, T., Goto, T., Tamayama, T., Kameno, Y., Wakuda, T., Kuwabara, H., Senju, A., Nishizawa, S., Ouchi, Y., Yamasue, H., 2022. Extrastriatal dopamine D2/3 receptor binding, functional connectivity, and autism socio-communicational deficits: a PET and fMRI study. Mol Psychiatry 27, 2106–2113. https://doi.org/10.1038/s41380-022-01464-3
Murphy, D., 2020. Autism: Implications for high secure psychiatric care and move towards best practice. Research in Developmental Disabilities 100, 103615. https://doi.org/10.1016/j.ridd.2020.103615
Murphy, D., 2007. Hare Psychopathy Checklist Revised profiles of male patients with Asperge's syndrome detained in high security psychiatric care. Journal of Forensic Psychiatry & Psychology - J FORENSIC PSYCHIATRY PSYCHOL 18, 120–126. https://doi.org/10.1080/14789940601014777
Murphy, D., Walker, F., Broyd, J., 2024. Do autism and psychopathy co-occur? A systematic review and clinical discussion. Criminal Behaviour & Mental Health 34, 411–430. https://doi.org/10.1002/cbm.2352
Murray, L., Waller, R., Hyde, L.W., 2018. A Systematic Review Examining the Link Between Psychopathic Personality Traits, Antisocial Behavior, and Neural Reactivity During Reward and Loss Processing. Personal Disord 9, 497–509. https://doi.org/10.1037/per0000308
Murrie, D.C., Cornell, D.G., Kaplan, S., McConville, D., Levy-Elkon, A., 2004. Psychopathy scores and violence among juvenile offenders: a multi-measure study. Behavioral Sci & The Law 22, 49–67. https://doi.org/10.1002/bsl.573
Nakamura, K., Sekine, Y., Ouchi, Y., Tsujii, M., Yoshikawa, E., Futatsubashi, M., Tsuchiya, K.J., Sugihara, G., Iwata, Y., Suzuki, K., Matsuzaki, H., Suda, S.,

Sugiyama, T., Takei, N., Mori, N., 2010. Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. Arch Gen Psychiatry 67, 59–68. https://doi.org/10.1001/archgenpsychiatry.2009.137
Narvaes, R., Martins de Almeida, R.M., 2014. Aggressive behavior and three neurotransmitters: dopamine, GABA, and serotonin—A review of the last 10 years. Psychology & Neuroscience 7, 601–607. https://doi.org/10.3922/j.psns.2014.4.20
Nebel, M.B., Eloyan, A., Barber, A.D., Mostofsky, S.H., 2014. Precentral gyrus functional connectivity signatures of autism. Front Syst Neurosci 8, 80. https://doi.org/10.3389/fnsys.2014.00080
Nebel, M.B., Joel, S.E., Muschelli, J., Barber, A.D., Caffo, B.S., Pekar, J.J., Mostofsky, S.H., 2012. Disruption of functional organization within the primary motor cortex in children with autism. Hum Brain Mapp 35, 567–580. https://doi.org/10.1002/hbm.22188
Nelson Aguiar, R.J., Vitacco, M.J., Porter Staats, M.L., Dzurny, T., 2023. Psychopathy and callous-unemotional traits in adolescence: A systematic review of cultural inclusion and meta-analysis of fMRI neural correlates. Journal of Criminal Justice 86, 102067. https://doi.org/10.1016/j.jcrimjus.2023.102067
Neufeld, J., Chakrabarti, B., 2016. Empathy Modulates the Rewarding Effect of Mimicry. Sci Rep 6, 27751. https://doi.org/10.1038/srep27751
Neufeld, J., Hsu, C.-T., Chakrabarti, B., 2019. Atypical Reward-Driven Modulation of Mimicry-Related Neural Activity in Autism. Front. Psychiatry 10. https://doi.org/10.3389/fpsyt.2019.00327
Neumann, C.S., Johansson, P.T., Hare, R.D., 2013. The Psychopathy Checklist-Revised (PCL-R), low anxiety, and fearlessness: A structural equation modeling analysis. Personality Disorders: Theory, Research, and Treatment 4, 129–137. https://doi.org/10.1037/a0027886
Nickl-Jockschat, T., Habel, U., Maria Michel, T., Manning, J., Laird, A.R., Fox, P.T., Schneider, F., Eickhoff, S.B., 2011. Brain structure anomalies in autism spectrum disorder—a meta-analysis of VBM studies using anatomic likelihood estimation. Hum Brain Mapp 33, 1470–1489. https://doi.org/10.1002/hbm.21299
Niedenthal, P.M., 2007. Embodying Emotion. Science 316, 1002–1005. https://doi.org/10.1126/science.1136930
Nieminen-von Wendt, T.S., Metsähonkala, L., Kulomäki, T.A., Aalto, S., Autti, T.H., Vanhala, R., Eskola, O., Bergman, J., Hietala, J.A., von Wendt, L.O., 2004. Increased presynaptic dopamine function in Asperger syndrome. NeuroReport 15, 757.
Nigg, J.T., 2017. Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. Journal of Child Psychology and Psychiatry 58, 361–383. https://doi.org/10.1111/jcpp.12675
Nummenmaa, L., Hirvonen, J., Parkkola, R., Hietanen, J.K., 2008. Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. NeuroImage 43, 571–580. https://doi.org/10.1016/j.neuroimage.2008.08.014
Nummenmaa, L., Lukkarinen, L., Sun, L., Putkinen, V., Seppälä, K., Karjalainen, T., Karlsson, H.K., Hudson, M., Venetjoki, N., Salomaa, M., Rautio, P., Hirvonen, J., Lauerma, H., Tiihonen, J., 2021. Brain Basis of Psychopathy

in Criminal Offenders and General Population. Cereb Cortex 31, 4104–4114. https://doi.org/10.1093/cercor/bhab072
Nummenmaa, L., Manninen, S., Tuominen, L., Hirvonen, J., Kalliokoski, K.K., Nuutila, P., Jääskeläinen, I.P., Hari, R., Dunbar, R.I.M., Sams, M., 2015. Adult attachment style is associated with cerebral μ-opioid receptor availability in humans: Opioids and Attachment. Hum. Brain Mapp. 36, 3621–3628. https://doi.org/10.1002/hbm.22866
Nummenmaa, L., Tuominen, L., 2018. Opioid system and human emotions. British Journal of Pharmacology 175, 2737–2749. https://doi.org/10.1111/bph.13812
Nummenmaa, L., Tuominen, L., Dunbar, R., Hirvonen, J., Manninen, S., Arponen, E., Machin, A., Hari, R., Jääskeläinen, I.P., Sams, M., 2016. Social touch modulates endogenous μ-opioid system activity in humans. NeuroImage 138, 242–247. https://doi.org/10.1016/j.neuroimage.2016.05.063
Oberman, L.M., Winkielman, P., Ramachandran, V.S., 2009. Slow echo: facial EMG evidence for the delay of spontaneous, but not voluntary, emotional mimicry in children with autism spectrum disorders. Developmental Science 12, 510–520. https://doi.org/10.1111/j.1467-7687.2008.00796.x
Oddi, D., Crusio, W.E., D'Amato, F.R., Pietropaolo, S., 2013. Monogenic mouse models of social dysfunction: Implications for autism. Behavioural Brain Research, SI:Neurobiology of Autism 251, 75–84. https://doi.org/10.1016/j.bbr.2013.01.002
Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 87, 9868–9872. https://doi.org/10.1073/pnas.87.24.9868
Olami, A., Peled-Avron, L., 2024. Effects of classical psychedelics on implicit and explicit emotional empathy and cognitive empathy: a meta-analysis of MET task. Sci Rep 14, 24480. https://doi.org/10.1038/s41598-024-74810-w
Oliver, L.D., Vieira, J.B., Neufeld, R.W.J., Dziobek, I., Mitchell, D.G.V., 2018. Greater involvement of action simulation mechanisms in emotional vs cognitive empathy. Soc Cogn Affect Neurosci 13, 367–380. https://doi.org/10.1093/scan/nsy013
O'Nions, E., Lima, C.F., Scott, S.K., Roberts, R., McCrory, E.J., Viding, E., 2017. Reduced Laughter Contagion in Boys at Risk for Psychopathy. Current Biology 27, 3049-3055.e4. https://doi.org/10.1016/j.cub.2017.08.062
O'Nions, E., Tick, B., Rijsdijk, F., Happé, F., Plomin, R., Ronald, A., Viding, E., 2015. Examining the Genetic and Environmental Associations between Autistic Social and Communication Deficits and Psychopathic Callous-Unemotional Traits. PLoS One 10. https://doi.org/10.1371/journal.pone.0134331
O'Nions, L., Sebastian, C., Mccrory, E., Chantiluke, K., Happe, F., Viding, E., 2014. Neural bases of Theory of Mind in children with autism spectrum disorders and children with conduct problems and callous-unemotional traits. Developmental Science 17. https://doi.org/10.1111/desc.12167
Oostermeijer, S., Whittle, S., Suo, C., Allen, N.B., Simmons, J.G., Vijayakumar, N., van de Ven, P.M., Jansen, L.M.C., Yücel, M., Popma, A., 2016. Trajectories of adolescent conduct problems in relation to cortical thickness development: a longitudinal MRI study. Transl Psychiatry 6, e841–e841. https://doi.org/10.1038/tp.2016.111

Osugo, M., Whitehurst, T., Shatalina, E., Townsend, L., O'Brien, O., Mak, T.L.A., McCutcheon, R., Howes, O., 2022. Dopamine partial agonists and prodopaminergic drugs for schizophrenia: Systematic review and meta-analysis of randomized controlled trials. Neuroscience & Biobehavioral Reviews 135, 104568. https://doi.org/10.1016/j.neubiorev.2022.104568
Oubrahim, L., Combalbert, N., 2021. Frequency and origin (reactive/proactive) of aggressive behavior in young people with intellectual disability and autism spectrum disorder. International Journal of Developmental Disabilities 67, 209–216. https://doi.org/10.1080/20473869.2019.1640972
Padilla-Coreano, N., Martínez-Rivera, F.J., 2025. How dopamine guides our social world. Pharmacological Reviews 77. https://doi.org/10.1016/j.pharmr.2025.100085
Padmanabhan, A., Lynch, C.J., Schaer, M., Menon, V., 2017. The Default Mode Network in Autism. Biol Psychiatry Cogn Neurosci Neuroimaging 2, 476–486. https://doi.org/10.1016/j.bpsc.2017.04.004
Pagnozzi, A.M., Conti, E., Calderoni, S., Fripp, J., Rose, S.E., 2018. A systematic review of structural MRI biomarkers in autism spectrum disorder: A machine learning perspective. Int J Dev Neurosci 71, 68–82. https://doi.org/10.1016/j.ijdevneu.2018.08.010
Panksepp, J., 1979. A neurochemical theory of autism. Trends in Neurosciences 2, 174–177. https://doi.org/10.1016/0166-2236(79)90071-7
Patriquin, M.A., DeRamus, T., Libero, L.E., Laird, A., Kana, R.K., 2016. Neuroanatomical and neurofunctional markers of social cognition in autism spectrum disorder. Hum Brain Mapp 37, 3957–3978. https://doi.org/10.1002/hbm.23288
Pavăl, D., 2017. A Dopamine Hypothesis of Autism Spectrum Disorder. Developmental Neuroscience 39, 355–360. https://doi.org/10.1159/000478725
Pavăl, D., Miclutia, I., 2021. The Dopamine Hypothesis of Autism Spectrum Disorder Revisited: Current Status and Future Prospects. Developmental Neuroscience 43, 1–11. https://doi.org/10.1159/000515751
Pellissier, L.P., Gandía, J., Laboute, T., Becker, J.A.J., Le Merrer, J., 2018. μ opioid receptor, social behaviour and autism spectrum disorder: reward matters. Br J Pharmacol 175, 2750–2769. https://doi.org/10.1111/bph.13808
Penagos-Corzo, J.C., Cosio van-Hasselt, M., Escobar, D., Vázquez-Roque, R.A., Flores, G., 2022. Mirror neurons and empathy-related regions in psychopathy: Systematic review, meta-analysis, and a working model. Social Neuroscience 17, 462–479. https://doi.org/10.1080/17470919.2022.2128868
Philip, R.C.M., Dauvermann, M.R., Whalley, H.C., Baynham, K., Lawrie, S.M., Stanfield, A.C., 2012. A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. Neuroscience & Biobehavioral Reviews 36, 901–942. https://doi.org/10.1016/j.neubiorev.2011.10.008
Philippi, C.L., Pujara, M.S., Motzkin, J.C., Newman, J., Kiehl, K.A., Koenigs, M., 2015. Altered Resting-State Functional Connectivity in Cortical Networks in Psychopathy. J. Neurosci. 35, 6068–6078. https://doi.org/10.1523/JNEUROSCI.5010-14.2015
Plavén-Sigray, P., Ikonen Victorsson, P., Santillo, A., Matheson, G.J., Lee, M., Collste, K., Fatouros-Bergman, H., Sellgren, C.M., Erhardt, S., Agartz, I., Halldin, C., Farde, L., Cervenka, S., 2022. Thalamic dopamine D2-receptor

availability in schizophrenia: a study on antipsychotic-naive patients with first-episode psychosis and a meta-analysis. Mol Psychiatry 27, 1233–1240. https://doi.org/10.1038/s41380-021-01349-x
Poeppl, T.B., Donges, M.R., Mokros, A., Rupprecht, R., Fox, P.T., Laird, A.R., Bzdok, D., Langguth, B., Eickhoff, S.B., 2019. A view behind the mask of sanity: meta-analysis of aberrant brain activity in psychopaths. Mol Psychiatry 24, 463–470. https://doi.org/10.1038/s41380-018-0122-5
Pouw, L.B.C., Rieffe, C., Oosterveld, P., Huskens, B., Stockmann, L., 2013. Reactive/proactive aggression and affective/cognitive empathy in children with ASD. Research in Developmental Disabilities 34, 1256–1266. https://doi.org/10.1016/j.ridd.2012.12.022
Preller, K.H., Herdener, M., Schilbach, L., Stämpfli, P., Hulka, L.M., Vonmoos, M., Ingold, N., Vogeley, K., Tobler, P.N., Seifritz, E., Quednow, B.B., 2014a. Functional changes of the reward system underlie blunted response to social gaze in cocaine users. Proc Natl Acad Sci U S A 111, 2842–2847. https://doi.org/10.1073/pnas.1317090111
Preller, K.H., Hulka, L.M., Vonmoos, M., Jenni, D., Baumgartner, M.R., Seifritz, E., Dziobek, I., Quednow, B.B., 2014b. Impaired emotional empathy and related social network deficits in cocaine users. Addiction Biology 19, 452–466. https://doi.org/10.1111/adb.12070
Preston, S.D., 2017. The rewarding nature of social contact. Science 357, 1353–1354. https://doi.org/10.1126/science.aao7192
Prochazkova, E., Kret, M.E., 2017. Connecting minds and sharing emotions through mimicry: A neurocognitive model of emotional contagion. Neuroscience & Biobehavioral Reviews 80, 99–114. https://doi.org/10.1016/j.neubiorev.2017.05.013
Pruim, R.H.R., Mennes, M., Buitelaar, J.K., Beckmann, C.F., 2015. Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. NeuroImage 112, 278–287. https://doi.org/10.1016/j.neuroimage.2015.02.063
Pu, W., Luo, Q., Jiang, Y., Gao, Y., Ming, Q., Yao, S., 2017. Alterations of Brain Functional Architecture Associated with Psychopathic Traits in Male Adolescents with Conduct Disorder. Sci Rep 7, 11349. https://doi.org/10.1038/s41598-017-11775-z
Putnam, P.T., Chang, S.W.C., 2022. Interplay between the oxytocin and opioid systems in regulating social behaviour. Philosophical Transactions of the Royal Society B 377, 20210050. https://doi.org/10.1098/rstb.2021.0050
Quednow, B.B., 2017. Social cognition and interaction in stimulant use disorders. Current Opinion in Behavioral Sciences 13, 55–62. https://doi.org/10.1016/j.cobeha.2016.10.001
Rada, P., Barson, J.R., Leibowitz, S.F., Hoebel, B.G., 2010. Opioids in the hypothalamus control dopamine and acetylcholine levels in the nucleus accumbens. Brain Res 1312, 1–9. https://doi.org/10.1016/j.brainres.2009.11.055
Rafiee, F., Rezvani Habibabadi, R., Motaghi, M., Yousem, D.M., Yousem, I.J., 2022. Brain MRI in Autism Spectrum Disorder: Narrative Review and Recent Advances. Journal of Magnetic Resonance Imaging 55, 1613–1624. https://doi.org/10.1002/jmri.27949
Raine, A., 2018. Antisocial Personality as a Neurodevelopmental Disorder. Annu. Rev. Clin. Psychol. 14, 259–289. https://doi.org/10.1146/annurev-clinpsy-050817-084819

Raine, A., Lencz, T., Taylor, K., Hellige, J.B., Bihrle, S., Lacasse, L., Lee, M., Ishikawa, S., Colletti, P., 2003. Corpus Callosum Abnormalities in Psychopathic Antisocial Individuals. Arch Gen Psychiatry 60, 1134–1142. https://doi.org/10.1001/archpsyc.60.11.1134
Rajendran, G., Mitchell, P., 2007. Cognitive theories of autism. Developmental Review 27, 224–260. https://doi.org/10.1016/j.dr.2007.02.001
Reeves, K.C., Shah, N., Muñoz, B., Atwood, B.K., 2022. Opioid Receptor-Mediated Regulation of Neurotransmission in the Brain. Front. Mol. Neurosci. 15. https://doi.org/10.3389/fnmol.2022.919773
Reiss, D., Grubin, D., Meux, C., 1999. Institutional performance of male 'psychopaths' in a high-security hospital. The Journal of Forensic Psychiatry 10, 290–299. https://doi.org/10.1080/09585189908403682
Reynolds, L.M., Flores, C., 2021. Mesocorticolimbic Dopamine Pathways Across Adolescence: Diversity in Development. Frontiers in Neural Circuits 15.
Riddle, K., Cascio, C.J., Woodward, N.D., 2017. Brain structure in autism: a voxel-based morphometry analysis of the Autism Brain Imaging Database Exchange (ABIDE). Brain Imaging Behav 11, 541–551. https://doi.org/10.1007/s11682-016-9534-5
Robinson, M.D., Bresin, K., 2014. Higher Levels of Psychopathy Predict Poorer Motor Control: Implications for Understanding the Psychopathy Construct. J Psychopathol Behav Assess 36, 201–210. https://doi.org/10.1007/s10862-013-9388-8
Rocchi, G., Sterlini, B., Tardito, S., Inglese, M., Corradi, A., Filaci, G., Amore, M., Magioncalda, P., Martino, M., 2020. Opioidergic System and Functional Architecture of Intrinsic Brain Activity: Implications for Psychiatric Disorders. Neuroscientist 26, 343–358. https://doi.org/10.1177/1073858420902360
Rogers, J., Viding, E., James Blair, R., Frith, U., Happé, F., 2006. Autism spectrum disorder and psychopathy: shared cognitive underpinnings or double hit? Psychol. Med. 36, 1789–1798. https://doi.org/10.1017/S0033291706008853
Rogers, J.C., De Brito, S.A., 2016. Cortical and Subcortical Gray Matter Volume in Youths With Conduct Problems: A Meta-analysis. JAMA Psychiatry 73, 64–72. https://doi.org/10.1001/jamapsychiatry.2015.2423
Romero-Martínez, Á., Sarrate-Costa, C., Moya-Albiol, L., 2022. Reactive vs proactive aggression: A differential psychobiological profile? Conclusions derived from a systematic review. Neurosci Biobehav Rev 136, 104626. https://doi.org/10.1016/j.neubiorev.2022.104626
Rosen, N.E., Lord, C., Volkmar, F.R., 2021. The Diagnosis of Autism: From Kanner to DSM-III to DSM-5 and Beyond. J Autism Dev Disord 51, 4253–4270. https://doi.org/10.1007/s10803-021-04904-1
Ross, J., Ross, J., Teesson, M., Ross, J., Teesson, M., Darke, S., Ross, J., Teesson, M., Darke, S., Lynskey, M., Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., Cooke, R., Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., Cooke, R., 2005. The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). Drug and Alcohol Review 24, 411–418. https://doi.org/10.1080/09595230500286039
Roy, A., Roy, M., Deb, S., Unwin, G., Roy, A., 2015. Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions

in children: a systematic review. Journal of Intellectual Disability Research 59, 293–306. https://doi.org/10.1111/jir.12122
Ryu, J., Oh, M., 2025. Positron Emission Tomography in Autism Spectrum Disorder: Current Status and Future Perspectives. Seminars in Nuclear Medicine, CNS 55, 605–615. https://doi.org/10.1053/j.semnuclmed.2025.06.003
Sahley, T.L., Panksepp, J., 1987. Brain opioids and autism: An updated analysis of possible linkages. J Autism Dev Disord 17, 201–216. https://doi.org/10.1007/BF01495056
Salekin, R.T., 2016. Psychopathy in childhood: Toward better informing the DSM–5 and ICD-11 conduct disorder specifiers. Personality Disorders: Theory, Research, and Treatment 7, 180–191. https://doi.org/10.1037/per0000150
Sánchez De Ribera, O., Kavish, N., Katz, I.M., Boutwell, B.B., 2019. Untangling Intelligence, Psychopathy, Antisocial Personality Disorder, and Conduct Problems: A Meta–Analytic Review. Eur J Pers 33, 529–564. https://doi.org/10.1002/per.2207
Sato, M., Nakai, N., Fujima, S., Choe, K.Y., Takumi, T., 2023. Social circuits and their dysfunction in autism spectrum disorder. Mol Psychiatry 28, 3194–3206. https://doi.org/10.1038/s41380-023-02201-0
Sato, W., Uono, S., 2019. The atypical social brain network in autism: advances in structural and functional MRI studies. Current Opinion in Neurology 32, 617–621. https://doi.org/10.1097/WCO.0000000000000713
Schalbroeck, R., de Geus-Oei, L.-F., Selten, J.-P., Yaqub, M., Schrantee, A., van Amelsvoort, T., Booij, J., van Velden, F.H.P., 2021a. Cerebral [18F]-FDOPA Uptake in Autism Spectrum Disorder and Its Association with Autistic Traits. Diagnostics (Basel) 11, 2404. https://doi.org/10.3390/diagnostics11122404
Schalbroeck, R., van Velden, F.H.P., de Geus-Oei, L.-F., Yaqub, M., van Amelsvoort, T., Booij, J., Selten, J.-P., 2021b. Striatal dopamine synthesis capacity in autism spectrum disorder and its relation with social defeat: an [18F]-FDOPA PET/CT study. Transl Psychiatry 11, 47. https://doi.org/10.1038/s41398-020-01174-w
Schilbach, L., 2016. Towards a second-person neuropsychiatry. Philos Trans R Soc Lond B Biol Sci 371, 20150081. https://doi.org/10.1098/rstb.2015.0081
Schilbach, L., Eickhoff, S.B., Rotarska-Jagiela, A., Fink, G.R., Vogeley, K., 2008. Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. Conscious Cogn 17, 457–467. https://doi.org/10.1016/j.concog.2008.03.013
Schirmer, A., 2018. Is the voice an auditory face? An ALE meta-analysis comparing vocal and facial emotion processing. Soc Cogn Affect Neurosci 13, 1–13. https://doi.org/10.1093/scan/nsx142
Schlüter, T., Winz, O., Henkel, K., Prinz, S., Rademacher, L., Schmaljohann, J., Dautzenberg, K., Cumming, P., Kumakura, Y., Rex, S., Mottaghy, F.M., Gründer, G., Vernaleken, I., 2013. The Impact of Dopamine on Aggression: An [^{18} F]-FDOPA PET Study in Healthy Males. J. Neurosci. 33, 16889–16896. https://doi.org/10.1523/JNEUROSCI.1398-13.2013
Schmid, Y., Bershad, A.K., 2024. Altered States and Social Bonds: Effects of MDMA and Serotonergic Psychedelics on Social Behavior as a Mechanism Underlying Substance-Assisted Therapy. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, Therapeutic Tripping: Mechanisms

Underlying the Clinical Potential of Psychedelics 9, 490–499. https://doi.org/10.1016/j.bpsc.2024.02.001
Schuetze, M., Park, M.T.M., Cho, I.Y., MacMaster, F.P., Chakravarty, M.M., Bray, S.L., 2016. Morphological Alterations in the Thalamus, Striatum, and Pallidum in Autism Spectrum Disorder. Neuropsychopharmacol 41, 2627–2637. https://doi.org/10.1038/npp.2016.64
Schuetze, M., Rohr, C.S., Dewey, D., McCrimmon, A., Bray, S., 2017. Reinforcement Learning in Autism Spectrum Disorder. Front. Psychol. 8. https://doi.org/10.3389/fpsyg.2017.02035
Schulte-Rüther, M., Greimel, E., Markowitsch, H.J., Kamp-Becker, I., Remschmidt, H., Fink, G.R., Piefke, M., 2011. Dysfunctions in brain networks supporting empathy: An fMRI study in adults with autism spectrum disorders. Social Neuroscience 6, 1–21. https://doi.org/10.1080/17470911003708032
Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J., 2014. Fractionating theory of mind: A meta-analysis of functional brain imaging studies. Neuroscience & Biobehavioral Reviews 42, 9–34. https://doi.org/10.1016/j.neubiorev.2014.01.009
Seeman, P., Wilson, A., Gmeiner, P., Kapur, S., 2006. Dopamine D2 and D3 receptors in human putamen, caudate nucleus, and globus pallidus. Synapse 60, 205–211. https://doi.org/10.1002/syn.20298
Seo, D., Patrick, C.J., Kennealy, P.J., 2008. Role of Serotonin and Dopamine System Interactions in the Neurobiology of Impulsive Aggression and its Comorbidity with other Clinical Disorders. Aggress Violent Behav 13, 383–395. https://doi.org/10.1016/j.avb.2008.06.003
Shaffer, J.J., Mani, M., Schmitz, S.L., Xu, J., Owusu, N., Wu, D., Magnotta, V.A., Wemmie, J.A., 2020. Proton Exchange Magnetic Resonance Imaging: Current and Future Applications in Psychiatric Research. Front. Psychiatry 11, 532606. https://doi.org/10.3389/fpsyt.2020.532606
Shamay-Tsoory, S.G., Aharon-Peretz, J., Perry, D., 2009. Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. Brain 132, 617–627. https://doi.org/10.1093/brain/awn279
Sims, T.B., Van Reekum, C.M., Johnstone, T., Chakrabarti, B., 2012. How reward modulates mimicry: EMG evidence of greater facial mimicry of more rewarding happy faces. Psychophysiology 49, 998–1004. https://doi.org/10.1111/j.1469-8986.2012.01377.x
Skuse, D.H., Gallagher, L., 2009. Dopaminergic-neuropeptide interactions in the social brain. Trends in Cognitive Sciences 13, 27–35. https://doi.org/10.1016/j.tics.2008.09.007
Smith, K.S., Tindell, A.J., Aldridge, J.W., Berridge, K.C., 2009. Ventral pallidum roles in reward and motivation. Behavioural Brain Research 196, 155–167. https://doi.org/10.1016/j.bbr.2008.09.038
Smitha, K., Akhil Raja, K., Arun, K., Rajesh, P., Thomas, B., Kapilamoorthy, T., Kesavadas, C., 2017. Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. Neuroradiol J 30, 305–317. https://doi.org/10.1177/1971400917697342
Soares, J., Marques, P., Alves, V., Sousa, N., 2013. A hitchhiker's guide to diffusion tensor imaging. Front. Neurosci. 7. https://doi.org/10.3389/fnins.2013.00031

Soares-Cunha, C., Coimbra, B., Sousa, N., Rodrigues, A.J., 2016. Reappraising striatal D1- and D2-neurons in reward and aversion. Neurosci Biobehav Rev 68, 370–386. https://doi.org/10.1016/j.neubiorev.2016.05.021
Song, Z., Jones, A., Corcoran, R., Daly, N., Abu-Akel, A., Gillespie, S.M., 2023. Psychopathic traits and theory of mind task performance: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews 151, 105231. https://doi.org/10.1016/j.neubiorev.2023.105231
Spitzer, R.L., Williams, J., Gibbon, M., First, M., 1992. The structured clinical interview for DSM-III-R (SCID). I: history, rationale, and description. Archives of general psychiatry 49, 624–9. https://doi.org/10.1001/archpsyc.1992.01820080032005)
Sreenivas, S., Boehm, S.G., Linden, D.E.J., 2012. Emotional faces and the default mode network. Neuroscience Letters 506, 229–234. https://doi.org/10.1016/j.neulet.2011.11.012
Stahl, S.M., 2001. "Dopamine System Stabilizers, Aripiprazole, and the Next Generation of Antipsychotics, Part 1: “Goldilocks” Actions at Dopamine Receptors: (Brainstorms). J. Clin. Psychiatry 62, 841–842. https://doi.org/10.4088/JCP.v62n1101
Stark, N., Bobadilla, L., Michael, P., Saturn, S., Portner, M., 2023. A meta-analytic review of the relationship between empathy and oxytocin: Implications for application in psychopathy research. Aggression and Violent Behavior 70, 101828. https://doi.org/10.1016/j.avb.2023.101828
Stavropoulos, K.K.M., Carver, L.J., 2013. Research Review: Social motivation and oxytocin in autism – implications for joint attention development and intervention. Journal of Child Psychology and Psychiatry 54, 603–618. https://doi.org/10.1111/jcpp.12061
Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., Frangou, S., 2011. Autism Spectrum Disorders and Schizophrenia: Meta-Analysis of the Neural Correlates of Social Cognition. PLoS One 6, e25322. https://doi.org/10.1371/journal.pone.0025322
Svensson, J.E., Schain, M., Plavén-Sigray, P., Cervenka, S., Tiger, M., Nord, M., Halldin, C., Farde, L., Lundberg, J., 2019. Validity and reliability of extrastriatal [11C]raclopride binding quantification in the living human brain. NeuroImage 202, 116143. https://doi.org/10.1016/j.neuroimage.2019.116143
Szczepanski, S.M., Knight, R.T., 2014. Insights into Human Behavior from Lesions to the Prefrontal Cortex. Neuron 83, 1002–1018. https://doi.org/10.1016/j.neuron.2014.08.011
Ta, C., Mj, W., 2011. Promoting imitation in young children with autism: a comparison of reciprocal imitation training and video modeling. Journal of autism and developmental disorders 41. https://doi.org/10.1007/s10803-010-1086-8
Takahashi, K., Mizuno, K., Sasaki, A.T., Wada, Y., Tanaka, M., Ishii, A., Tajima, K., Tsuyuguchi, N., Watanabe, K., Zeki, S., Watanabe, Y., 2015. Imaging the passionate stage of romantic love by dopamine dynamics. Front Hum Neurosci 9, 191. https://doi.org/10.3389/fnhum.2015.00191
Tamon, H., Fujino, J., Itahashi, T., Frahm, L., Parlatini, V., Aoki, Y.Y., Castellanos, F.X., Eickhoff, S.B., Cortese, S., 2024. Shared and Specific Neural Correlates of Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder: A Meta-Analysis of 243 Task-Based Functional MRI

Studies. Am J Psychiatry 181, 541–552. https://doi.org/10.1176/appi.ajp.20230270
Tan, Z., Wei, H., Song, X., Mai, W., Yan, J., Ye, W., Ling, X., Hou, L., Zhang, S., Yan, S., Xu, H., Wang, L., 2022. Positron Emission Tomography in the Neuroimaging of Autism Spectrum Disorder: A Review. Front Neurosci 16, 806876. https://doi.org/10.3389/fnins.2022.806876
Terbeck, S., Savulescu, J., Chesterman, L.P., Cowen, P.J., 2016. Noradrenaline effects on social behaviour, intergroup relations, and moral decisions. Neuroscience & Biobehavioral Reviews 66, 54–60. https://doi.org/10.1016/j.neubiorev.2016.03.031
Thapar, A., Cooper, M., Rutter, M., 2017. Neurodevelopmental disorders. The Lancet Psychiatry 4, 339–346. https://doi.org/10.1016/S2215-0366(16)30376-5
Tholen, M.G., Trautwein, F.-M., Böckler, A., Singer, T., Kanske, P., 2020. Functional magnetic resonance imaging (fMRI) item analysis of empathy and theory of mind. Human Brain Mapping 41, 2611–2628. https://doi.org/10.1002/hbm.24966
Tick, B., Bolton, P., Happé, F., Rutter, M., Rijsdijk, F., 2016. Heritability of autism spectrum disorders: a meta-analysis of twin studies. J Child Psychol Psychiatry 57, 585–595. https://doi.org/10.1111/jcpp.12499
Tiihonen, J., Koskuvi, M., Lähteenvuo, M., Virtanen, P.L.J., Ojansuu, I., Vaurio, O., Gao, Y., Hyötyläinen, I., Puttonen, K.A., Repo-Tiihonen, E., Paunio, T., Rautiainen, M.-R., Tyni, S., Koistinaho, J., Lehtonen, Š., 2020. Neurobiological roots of psychopathy. Mol Psychiatry 25, 3432–3441. https://doi.org/10.1038/s41380-019-0488-z
Tillem, S., Brennan, G., Wu, J., Mayes, L., Baskin-Sommers, A., 2019. Alpha response reveals attention abnormalities in psychopathy. Personality Disorders: Theory, Research, and Treatment 10, 291–296. https://doi.org/10.1037/per0000314
Timmers, I., Park, A.L., Fischer, M.D., Kronman, C.A., Heathcote, L.C., Hernandez, J.M., Simons, L.E., 2018. Is Empathy for Pain Unique in Its Neural Correlates? A Meta-Analysis of Neuroimaging Studies of Empathy. Front. Behav. Neurosci. 12. https://doi.org/10.3389/fnbeh.2018.00289
Tobler, P.N., Preller, K.H., Campbell-Meiklejohn, D.K., Kirschner, M., Kraehenmann, R., Stämpfli, P., Herdener, M., Seifritz, E., Quednow, B.B., 2016. Shared neural basis of social and non-social reward deficits in chronic cocaine users. Soc Cogn Affect Neurosci 11, 1017–1025. https://doi.org/10.1093/scan/nsw030
Tomasino, B., Gremese, M., 2016. The Cognitive Side of M1. Front. Hum. Neurosci. 10. https://doi.org/10.3389/fnhum.2016.00298
Tonizzi, I., Giofrè, D., Usai, M.C., 2022. Inhibitory Control in Autism Spectrum Disorders: Meta-analyses on Indirect and Direct Measures. Journal of Autism & Developmental Disorders 52, 4949–4965. https://doi.org/10.1007/s10803-021-05353-6
Tortora, F., Hadipour, A.L., Battaglia, S., Falzone, A., Avenanti, A., Vicario, C.M., 2023. The Role of Serotonin in Fear Learning and Memory: A Systematic Review of Human Studies. Brain Sciences 13, 1197. https://doi.org/10.3390/brainsci13081197
Trevisan, D.A., Foss-Feig, J.H., Naples, A.J., Srihari, V., Anticevic, A., McPartland, J.C., 2020. Autism Spectrum Disorder and Schizophrenia Are Better

Differentiated by Positive Symptoms Than Negative Symptoms. Front. Psychiatry 11. https://doi.org/10.3389/fpsyt.2020.00548
Trundle, G., Jones, K.A., Ropar, D., Egan, V., 2023. Prevalence of Victimisation in Autistic Individuals: A Systematic Review and Meta-Analysis. Trauma, Violence, & Abuse 24, 2282–2296. https://doi.org/10.1177/15248380221093689
Ttofi, M.M., Farrington, D.P., Piquero, A.R., Lösel, F., DeLisi, M., Murray, J., 2016. Intelligence as a protective factor against offending: A meta-analytic review of prospective longitudinal studies. Journal of Criminal Justice, 'Protective Factors against Youth Offending and Violence: Results from Prospective Longitudinal Studies' 45, 4–18. https://doi.org/10.1016/j.jcrimjus.2016.02.003
Tully, J., Cross, B., Gerrie, B., Griem, J., Blackwood, N., Blair, R.J., McCutcheon, R.A., 2023a. A systematic review and meta-analysis of brain volume abnormalities in disruptive behaviour disorders, antisocial personality disorder and psychopathy. Nat. Mental Health 1, 163–173. https://doi.org/10.1038/s44220-023-00032-0
Tully, J., Frey, A., Fotiadou, M., Kolla, N.J., Eisenbarth, H., 2023b. Psychopathy in women: insights from neuroscience and ways forward for research. CNS Spectrums 28, 120–132. https://doi.org/10.1017/S1092852921001085
Tully, J., Sethi, A., Griem, J., Paloyelis, Y., Craig, M.C., Williams, S.C.R., Murphy, D., Blair, R.J., Blackwood, N., 2023c. Oxytocin normalizes the implicit processing of fearful faces in psychopathy: a randomized crossover study using fMRI. Nat. Mental Health 1, 420–427. https://doi.org/10.1038/s44220-023-00067-3
Turtonen, O., Saarinen, A., Nummenmaa, L., Tuominen, L., Tikka, M., Armio, R.-L., Hautamäki, A., Laurikainen, H., Raitakari, O., Keltikangas-Järvinen, L., Hietala, J., 2021. Adult Attachment System Links With Brain Mu Opioid Receptor Availability In Vivo. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 6, 360–369. https://doi.org/10.1016/j.bpsc.2020.10.013
Tuvblad, C., Bezdjian, S., Raine, A., Baker, L.A., 2014. The Heritability of Psychopathic Personality in 14 to 15 year Old Twins: A Multi-Rater, Multi-Measure Approach. Psychol Assess 26, 704–716. https://doi.org/10.1037/a0036711
Tuvblad, C., Fanti, K.A., Andershed, H., Colins, O.F., Larsson, H., 2017. Psychopathic personality traits in 5 year old twins: the importance of genetic and shared environmental influences. Eur Child Adolesc Psychiatry 26, 469–479. https://doi.org/10.1007/s00787-016-0899-1
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. NeuroImage 15, 273–289. https://doi.org/10.1006/nimg.2001.0978
Uljarevic, M., Hamilton, A., 2013. Recognition of Emotions in Autism: A Formal Meta-Analysis. J Autism Dev Disord 43, 1517–1526. https://doi.org/10.1007/s10803-012-1695-5
Umbach, R.H., Tottenham, N., 2021. Callous-unemotional traits and reduced default mode network connectivity within a community sample of children. Development and Psychopathology 33, 1170–1183. https://doi.org/10.1017/S0954579420000401

Umukoro, S., Aladeokin, A.C., Eduviere, A.T., 2013. Aggressive behavior: A comprehensive review of its neurochemical mechanisms and management. Aggression and Violent Behavior 18, 195–203. https://doi.org/10.1016/j.avb.2012.11.002
van de Giessen, E., Rosell, D.R., Thompson, J.L., Xu, X., Girgis, R.R., Ehrlich, Y., Slifstein, M., Abi-Dargham, A., Siever, L.J., 2014. Serotonin transporter availability in impulsive aggressive personality disordered patients: A PET study with [11C]DASB. Journal of Psychiatric Research 58, 147–154. https://doi.org/10.1016/j.jpsychires.2014.07.025
van den Heuvel, M.P., Hulshoff Pol, H.E., 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 20, 519–534. https://doi.org/10.1016/j.euroneuro.2010.03.008
van der Schalk, J., Hawk, S.T., Fischer, A.H., Doosje, B., 2011. Moving faces, looking places: Validation of the Amsterdam Dynamic Facial Expression Set (ADFES). Emotion 11, 907–920. https://doi.org/10.1037/a0023853
Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Hum Brain Mapp 30, 829–858. https://doi.org/10.1002/hbm.20547
Van Overwalle, F., D'aes, T., Mariën, P., 2015. Social cognition and the cerebellum: A meta-analytic connectivity analysis. Hum Brain Mapp 36, 5137–5154. https://doi.org/10.1002/hbm.23002
Van Rooij, D., Anagnostou, E., Arango, C., Auzias, G., Behrmann, M., Busatto, G.F., Calderoni, S., Daly, E., Deruelle, C., Di Martino, A., Dinstein, I., Duran, F.L.S., Durston, S., Ecker, C., Fair, D., Fedor, J., Fitzgerald, J., Freitag, C.M., Gallagher, L., Gori, I., Haar, S., Hoekstra, L., Jahanshad, N., Jalbrzikowski, M., Janssen, J., Lerch, J., Luna, B., Martinho, M.M., McGrath, J., Muratori, F., Murphy, C.M., Murphy, D.G.M., O'Hearn, K., Oranje, B., Parellada, M., Retico, A., Rosa, P., Rubia, K., Shook, D., Taylor, M., Thompson, P.M., Tosetti, M., Wallace, G.L., Zhou, F., Buitelaar, J.K., 2018. Cortical and Subcortical Brain Morphometry Differences Between Patients With Autism Spectrum Disorder and Healthy Individuals Across the Lifespan: Results From the ENIGMA ASD Working Group. AJP 175, 359–369. https://doi.org/10.1176/appi.ajp.2017.17010100
van Schalkwyk, G.I., Beyer, C., Johnson, J., Deal, M., Bloch, M.H., 2018. Antipsychotics for aggression in adults: A meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry 81, 452–458. https://doi.org/10.1016/j.pnpbp.2017.07.019
van Veluw, S.J., Chance, S.A., 2014. Differentiating between self and others: an ALE meta-analysis of fMRI studies of self-recognition and theory of mind. Brain Imaging Behav 8, 24–38. https://doi.org/10.1007/s11682-013-9266-8
Vanderschuren, L.J.M.J., Achterberg, E.J.M., Trezza, V., 2016. The neurobiology of social play and its rewarding value in rats. Neuroscience & Biobehavioral Reviews 70, 86–105. https://doi.org/10.1016/j.neubiorev.2016.07.025
Verel, I., Visser, G.W.M., Dongen, G.A. van, 2005. The Promise of Immuno-PET in Radioimmunotherapy. Journal of Nuclear Medicine 46, 164S-171S.
Verhoeff, B., 2013. Autism in flux: a history of the concept from Leo Kanner to *DSM-5*. Hist Psychiatry 24, 442–458. https://doi.org/10.1177/0957154X13500584
Verschuere, B., te Kaat, L., 2020. What Are the Core Features of Psychopathy? A Prototypicality Analysis Using the Psychopathy Checklist-Revised (PCL-R).

Journal of Personality Disorders 34, 410–419. https://doi.org/10.1521/pedi_2019_33_396
Viskontas, I.V., Possin, K.L., Miller, B.L., 2007. Symptoms of Frontotemporal Dementia Provide Insights into Orbitofrontal Cortex Function and Social Behavior. Annals of the New York Academy of Sciences 1121, 528–545. https://doi.org/10.1196/annals.1401.025
Volkmar, F.R., Reichow, B., 2013. Autism in DSM-5: progress and challenges. Mol Autism 4, 13. https://doi.org/10.1186/2040-2392-4-13
Volkow, N.D., Fowler, J.S., Wang, G.J., Baler, R., Telang, F., 2009. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56, 3–8. https://doi.org/10.1016/j.neuropharm.2008.05.022
Volynets, S., Smirnov, D., Saarimäki, H., Nummenmaa, L., 2020. Statistical pattern recognition reveals shared neural signatures for displaying and recognizing specific facial expressions. Social Cognitive and Affective Neuroscience 15, 803–813. https://doi.org/10.1093/scan/nsaa110
Wagner, N.J., Waller, R., Flom, M., Ronfard, S., Fenstermacher, S., Saudino, K., 2020. Less imitation of arbitrary actions is a specific developmental precursor to callous-unemotional traits in early childhood. J Child Psychol Psychiatry 61, 818–825. https://doi.org/10.1111/jcpp.13182
Walker, M.A., 2008. Treatment of autism spectrum disorders: neurotransmitter signaling pathways involved in motivation and reward as therapeutic targets. Expert Opinion on Therapeutic Targets 12, 949–967. https://doi.org/10.1517/14728222.12.8.949
Wallace, G.L., Dankner, N., Kenworthy, L., Giedd, J.N., Martin, A., 2010. Age-related temporal and parietal cortical thinning in autism spectrum disorders. Brain 133, 3745–3754. https://doi.org/10.1093/brain/awq279
Wallace, G.L., Shaw, P., Lee, N.R., Clasen, L.S., Raznahan, A., Lenroot, R.K., Martin, A., Giedd, J.N., 2012. Distinct Cortical Correlates of Autistic versus Antisocial Traits in a Longitudinal Sample of Typically Developing Youth. J Neurosci 32, 4856–4860. https://doi.org/10.1523/JNEUROSCI.6214-11.2012
Wallace, L., Fido, D., Sumich, A.L., Heym, N., 2022. A systematic review on the current conceptualisations of successful psychopathy. Forensic Science International: Mind and Law 3, 100076. https://doi.org/10.1016/j.fsiml.2022.100076
Waller, R., Dotterer, H.L., Murray, L., Maxwell, A.M., Hyde, L.W., 2017. White-matter tract abnormalities and antisocial behavior: A systematic review of diffusion tensor imaging studies across development. NeuroImage: Clinical 14, 201–215. https://doi.org/10.1016/j.nicl.2017.01.014
Wallis, K., Kelly, M., McRae, S.E., McDonald, S., Campbell, L.E., 2022. Domains and measures of social cognition in acquired brain injury: A scoping review. Neuropsychol Rehabil 32, 2429–2463. https://doi.org/10.1080/09602011.2021.1933087
Walsh, J.J., Christoffel, D.J., Malenka, R.C., 2023. Neural circuits regulating prosocial behaviors. Neuropsychopharmacol. 48, 79–89. https://doi.org/10.1038/s41386-022-01348-8
Wandschneider, B., Koepp, M.J., 2016. Pharmaco fMRI: Determining the functional anatomy of the effects of medication. NeuroImage: Clinical 12, 691–697. https://doi.org/10.1016/j.nicl.2016.10.002
Wang, Q., Li, H.-Y., Li, Y.-D., Lv, Y.-T., Ma, H.-B., Xiang, A.-F., Jia, X.-Z., Liu, D.-Q., 2021. Resting-state abnormalities in functional connectivity of the

default mode network in autism spectrum disorder: a meta-analysis. Brain Imaging and Behavior 15, 2583–2592. https://doi.org/10.1007/s11682-021-00460-5
Wang, W., Liu, J., Shi, S., Liu, T., Ma, L., Ma, X., Tian, J., Gong, Q., Wang, M., 2018. Altered Resting-State Functional Activity in Patients With Autism Spectrum Disorder: A Quantitative Meta-Analysis. Front. Neurol. 9. https://doi.org/10.3389/fneur.2018.00556
Wang, Y., Metoki, A., Alm, K.H., Olson, I.R., 2018. White matter pathways and social cognition. Neurosci Biobehav Rev 90, 350–370. https://doi.org/10.1016/j.neubiorev.2018.04.015
Wang, Y., Shang, S., Xie, W., Hong, S., Liu, Z., Su, Y., 2023. The relation between aggression and theory of mind in children: A meta-analysis. Developmental Science 26, e13310. https://doi.org/10.1111/desc.13310
Wardle, M.C., Bershad, A.K., de Wit, H., 2016. Naltrexone alters the processing of social and emotional stimuli in healthy adults. Social Neuroscience 11, 579–591. https://doi.org/10.1080/17470919.2015.1136355
Weiland, B.J., Heitzeg, M.M., Zald, D., Cummiford, C., Love, T., Zucker, R.A., Zubieta, J.-K., 2014. Relationship between impulsivity, prefrontal anticipatory activation, and striatal dopamine release during rewarded task performance. Psychiatry Research: Neuroimaging 223, 244–252. https://doi.org/10.1016/j.pscychresns.2014.05.015
Weinstein, A.M., 2023. Reward, motivation and brain imaging in human healthy participants - A narrative review. Front Behav Neurosci 17, 1123733. https://doi.org/10.3389/fnbeh.2023.1123733
Weisz, E., Zaki, J., 2018. Motivated empathy: a social neuroscience perspective. Current Opinion in Psychology 24, 67–71. https://doi.org/10.1016/j.copsyc.2018.05.005
Wenzel, B., Mollitor, J., Deuther-Conrad, W., Dukic-Stefanovic, S., Kranz, M., Vraka, C., Teodoro, R., Günther, R., Donat, C.K., Ludwig, F.-A., Fischer, S., Smits, R., Wadsak, W., Mitterhauser, M., Steinbach, J., Hoepping, A., Brust, P., 2016. Development of a Novel Nonpeptidic^{18} F-Labeled Radiotracer for in Vivo Imaging of Oxytocin Receptors with Positron Emission Tomography. J. Med. Chem. 59, 1800–1817. https://doi.org/10.1021/acs.jmedchem.5b01080
Whitwell, J.L., 2009. Voxel-Based Morphometry: An Automated Technique for Assessing Structural Changes in the Brain. J Neurosci 29, 9661–9664. https://doi.org/10.1523/JNEUROSCI.2160-09.2009
Wigham, S., Rodgers, J., Berney, T., Le Couteur, A., Ingham, B., Parr, J.R., 2019. Psychometric properties of questionnaires and diagnostic measures for autism spectrum disorders in adults: A systematic review. Autism 23, 287–305. https://doi.org/10.1177/1362361317748245
Wild, B., Erb, M., Bartels, M., 2001. Are emotions contagious? Evoked emotions while viewing emotionally expressive faces: quality, quantity, time course and gender differences. Psychiatry Research 102, 109–124. https://doi.org/10.1016/S0165-1781(01)00225-6
Winter, K., Spengler, S., Bermpohl, F., Singer, T., Kanske, P., 2017. Social cognition in aggressive offenders: Impaired empathy, but intact theory of mind. Sci Rep 7, 670. https://doi.org/10.1038/s41598-017-00745-0
Winters, D.E., Sakai, J.T., Carter, R.M., 2021. Resting-state network topology characterizing callous-unemotional traits in adolescence. NeuroImage: Clinical 32, 102878. https://doi.org/10.1016/j.nicl.2021.102878

Wiskerke, J., Schetters, D., van Es, I.E., van Mourik, Y., den Hollander, B.R.O., Schoffelmeer, A.N.M., Pattij, T., 2011. μ-Opioid Receptors in the Nucleus Accumbens Shell Region Mediate the Effects of Amphetamine on Inhibitory Control But Not Impulsive Choice. J Neurosci 31, 262–272. https://doi.org/10.1523/JNEUROSCI.4794-10.2011
Woodbury-Smith, M., Scherer, S.W., 2018. Progress in the genetics of autism spectrum disorder. Developmental Medicine & Child Neurology 60, 445–451. https://doi.org/10.1111/dmcn.13717
Woodworth, M., Waschbusch, D., 2008. Emotional processing in children with conduct problems and callous/unemotional traits. Child: Care, Health and Development 34, 234–244. https://doi.org/10.1111/j.1365-2214.2007.00792.x
World Health Organization. (2016). International statistical classification of diseases and related health problems (10th ed.). https://icd.who.int/browse10/2016/en
Wu, T., Barnes, J.C., 2013. Two dopamine receptor genes (*DRD2* and *DRD4*) predict psychopathic personality traits in a sample of American adults. Journal of Criminal Justice 41, 188–195. https://doi.org/10.1016/j.jcrimjus.2013.02.001
Xiao, H., Jacobsen, A., Chen, Z., Wang, Y., 2017. Detecting social-cognitive deficits after traumatic brain injury: An ALE meta-analysis of fMRI studies. Brain Injury 31, 1331–1339. https://doi.org/10.1080/02699052.2017.1319576
Yang, J., Hofmann, J., 2016. Action observation and imitation in autism spectrum disorders: an ALE meta-analysis of fMRI studies. Brain Imaging Behav 10, 960–969. https://doi.org/10.1007/s11682-015-9456-7
Yang, X., Si, T., Gong, Q., Qiu, L., Jia, Z., Zhou, M., Zhao, Y., Hu, X., Wu, M., Zhu, H., 2016. Brain gray matter alterations and associated demographic profiles in adults with autism spectrum disorder: A meta-analysis of voxel-based morphometry studies. Aust N Z J Psychiatry 50, 741–753. https://doi.org/10.1177/0004867415623858
Yang, Y., Raine, A., 2009. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: A meta-analysis. Psychiatry Research: Neuroimaging 174, 81–88. https://doi.org/10.1016/j.pscychresns.2009.03.012
Yang, Y., Wang, P., Baker, L.A., Narr, K.L., Joshi, S.H., Hafzalla, G., Raine, A., Thompson, P.M., 2015. Thicker Temporal Cortex Associates with a Developmental Trajectory for Psychopathic Traits in Adolescents. PLoS ONE 10, e0127025. https://doi.org/10.1371/journal.pone.0127025
Yanowitch, R., Coccaro, E.F., 2011. The Neurochemistry of Human Aggression, in: Advances in Genetics. Elsevier, pp. 151–169. https://doi.org/10.1016/B978-0-12-380858-5.00005-8
Yazgeç, E., Bora, E., İngeç, S., Çıray, R.O., Bağcı, B., Alkın, T., 2023. Social Cognition in Opioid Use Disorder. Subst Use Misuse 58, 996–1003. https://doi.org/10.1080/10826084.2023.2201845
Yildirim, B.O., Derksen, J.J.L., 2015a. Mesocorticolimbic dopamine functioning in primary psychopathy: A source of within-group heterogeneity. Psychiatry Research 229, 633–677. https://doi.org/10.1016/j.psychres.2015.07.005
Yildirim, B.O., Derksen, J.J.L., 2015b. Clarifying the heterogeneity in psychopathic samples: Towards a new continuum of primary and secondary psychopathy. Aggression and Violent Behavior 24, 9–41. https://doi.org/10.1016/j.avb.2015.05.001

Yildirim, B.O., Derksen, J.J.L., 2013. Systematic review, structural analysis, and new theoretical perspectives on the role of serotonin and associated genes in the etiology of psychopathy and sociopathy. Neuroscience & Biobehavioral Reviews 37, 1254–1296. https://doi.org/10.1016/j.neubiorev.2013.04.009
Yuan, P., Raz, N., 2014. Prefrontal cortex and executive functions in healthy adults: A meta-analysis of structural neuroimaging studies. Neuroscience & Biobehavioral Reviews 42, 180–192. https://doi.org/10.1016/j.neubiorev.2014.02.005
Zablocki-Thomas, P.B., Rogers, F.D., Bales, K.L., 2022. Neuroimaging of human and non-human animal emotion and affect in the context of social relationships. Front. Behav. Neurosci. 16. https://doi.org/10.3389/fnbeh.2022.994504
Zhang, R., Geng, X., Lee, T.M.C., 2017. Large-scale functional neural network correlates of response inhibition: an fMRI meta-analysis. Brain Struct Funct 222, 3973–3990. https://doi.org/10.1007/s00429-017-1443-x
Zhao, Y., Yang, L., Gong, G., Cao, Q., Liu, J., 2022. Identify aberrant white matter microstructure in ASD, ADHD and other neurodevelopmental disorders: A meta-analysis of diffusion tensor imaging studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry 113, 110477. https://doi.org/10.1016/j.pnpbp.2021.110477
Zielinski, B.A., Prigge, M.B.D., Nielsen, J.A., Froehlich, A.L., Abildskov, T.J., Anderson, J.S., Fletcher, P.T., Zygmunt, K.M., Travers, B.G., Lange, N., Alexander, A.L., Bigler, E.D., Lainhart, J.E., 2014. Longitudinal changes in cortical thickness in autism and typical development. Brain 137, 1799–1812. https://doi.org/10.1093/brain/awu083
Ziomkiewicz-Wichary, A., 2016. Serotonin and Dominance, in: Weekes-Shackelford, V., Shackelford, T.K., Weekes-Shackelford, V.A. (Eds.), Encyclopedia of Evolutionary Psychological Science. Springer International Publishing, Cham, pp. 1–4. https://doi.org/10.1007/978-3-319-16999-6_1440-1
Zürcher, N.R., Bhanot, A., McDougle, C.J., Hooker, J.M., 2015. A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: Current state and future research opportunities. Neuroscience & Biobehavioral Reviews 52, 56–73. https://doi.org/10.1016/j.neubiorev.2015.02.002
Zürcher, N.R., Walsh, E.C., Phillips, R.D., Cernasov, P.M., Tseng, C.-E.J., Dharanikota, A., Smith, E., Li, Z., Kinard, J.L., Bizzell, J.C., Greene, R.K., Dillon, D., Pizzagalli, D.A., Izquierdo-Garcia, D., Truong, K., Lalush, D., Hooker, J.M., Dichter, G.S., 2021. A simultaneous [11C]raclopride positron emission tomography and functional magnetic resonance imaging investigation of striatal dopamine binding in autism. Transl Psychiatry 11, 33. https://doi.org/10.1038/s41398-020-01170-0
Zweifel, L.S., Parker, J.G., Lobb, C.J., Rainwater, A., Wall, V.Z., Fadok, J.P., Darvas, M., Kim, M.J., Mizumori, S.J.Y., Paladini, C.A., Phillips, P.E.M., Palmiter, R.D., 2009. Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior. Proc. Natl. Acad. Sci. U.S.A. 106, 7281–7288. https://doi.org/10.1073/pnas.0813415106

Original publications

I

NeuroImage: Clinical 35 (2022) 103116

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Brain structural alterations in autism and criminal psychopathy

Tuomo Noppari [a,b,*], Lihua Sun [a,c], Lasse Lukkarinen [a], Vesa Putkinen [a], Pekka Tani [b], Nina Lindberg [d], Emma Saure [e,f], Hannu Lauerma [g,h], Jari Tiihonen [i,j,k], Niina Venetjoki [g], Marja Salomaa [g], Päivi Rautio [g], Jussi Hirvonen [l], Juha Salmi [m], Lauri Nummenmaa [a,n]

[a] Turku PET Centre, University of Turku, Turku, Finland
[b] Department of Psychiatry, Helsinki University Hospital, Helsinki, Finland
[c] Department of Nuclear Medicine, Huashan Hospital, Fudan University, Shanghai, China
[d] Department of Forensic Psychiatry, Helsinki University Hospital, Helsinki, Finland
[e] Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[f] BABA Center and Department of Clinical Neurophysiology, Children's Hospital, Helsinki University Hospital and University of Helsinki, Finland
[g] Psychiatric Hospital for Prisoners, Health Care Services for Prisoners, Turku, Finland
[h] Department of Forensic Psychiatry, Turku University Central Hospital, Finland
[i] Department of Clinical Neuroscience, Karolinska Institute and Center for Psychiatry Research, Stockholm, Sweden
[j] Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland
[k] Neuroscience Center, University of Helsinki, Helsinki, Finland
[l] Department of Radiology, Turku University Hospital, Turku, Finland
[m] Department of Neuroscience and Biomedical Engineering, School of Science, Aalto University, Espoo, Finland
[n] Department of Psychology, University of Turku, Turku, Finland

ARTICLE INFO

Keywords:
Social brain networks
Social cognition
Voxel-based morphometry
Pre-motor cortex
Frontotemporal cortex
Empathy

ABSTRACT

The goal of this study was to elucidate the anatomical brain basis of social cognition through two disorders with distinctively different phenotypes of social interaction. We compared structural MR images of 20 individuals with autism spectrum disorder (ASD), 19 violent offenders with high psychopathic traits, and 19 control participants using voxel-based morphometry (VBM). Our earlier study showed lower grey matter volume (GMV) values in the insula, frontal cortex, and sensorimotor cortex of the offender group compared to controls. In the present study, the images of the ASD group revealed lower GMV in the left precuneus, right cerebellum, and right precentral gyrus in comparison with controls. The comparison between the offender and ASD groups showed lower GMV values for the right temporal pole and left inferior frontal gyrus in the offender group. There was also an overlap of both disorders in the right pre-central cortex, showing lower GMV compared to controls. Our findings suggest structural differences between violent offenders with high psychopathy traits and ASD individuals in the frontotemporal social brain network areas, previously associated with empathy. We also provide evidence of similar abnormal structures in the motor cortex for both of these disorders, possibly related to uniting issues of social cognition.

1. Introduction

Brain networks for human social processing encompass large-scale circuits across all cerebral lobes, the cerebellum, and subcortical areas, such as the striatum and amygdala (Amodio and Frith, 2006; Fernández et al., 2018; Sato and Uono, 2019; Van Overwalle et al., 2015). The somatosensory areas and the inferior occipital gyrus (IOG), fusiform gyrus (FG), and superior temporal sulcus (STS) are involved, for instance, in recognizing and interpreting different socially relevant cues (Fernández et al., 2018; Lahnakoski et al., 2012; Nummenmaa and Calder, 2009; Sato and Uono, 2019). The posterior STS and temporo-parietal junction (TPJ), along with the temporal poles and several areas of the prefrontal cortex (PFC), are involved in reading others' thoughts (theory of mind), mentalizing, and empathy (Amodio and Frith, 2006; Blakemore, 2012). The inferior frontal gyrus (IFG) has been linked with emotional empathy and the ability to understand and resonate with the actions of others, and it is functionally connected with STS and the inferior parietal lobule (IPL) (Fitzgerald, 2019; Sato and

* Corrensponding author at: Department of Psychiatry, Helsinki University Hospital, PL, 590, 00029 HUS, Helsinki, Finland.
E-mail address: tuomo.noppari@hus.fi (T. Noppari).

https://doi.org/10.1016/j.nicl.2022.103116
Received 19 January 2022; Received in revised form 9 July 2022; Accepted 11 July 2022
Available online 13 July 2022
2213-1582/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Uono, 2019). In turn, the ventromedial prefrontal cortex is considered to be involved in the cognitive component of empathy (Fitzgerald, 2019). Autism and psychopathy are two distinctively different disorders involving aberrant socioemotional processing, and structural and functional alterations in the brain networks that support these functions (Sato and Uono, 2019). However, the exact differences in the brain networks across these two disorders remain unknown.

1.1. Abnormalities in frontotemporal, parietal and cerebellar areas of ASD

Autism spectrum disorder (ASD) is a heterogenous neurodevelopmental disorder with impairments in various social cognitive functions. According to DSM-5, the core features of ASD are: A) persistent deficits in social communication and social interaction B) restricted, repetitive patterns of behavior, interests, or activities. The cerebral anatomical findings in ASD have been heterogenous with a limited number of consistent abnormalities (Ecker et al., 2013; Pagnozzi et al., 2018; Riddle et al., 2017). One prominent neuropathologic theory suggests that anatomic abnormalities in ASD are age-specific (Courchesne et al., 2007; Courchesne et al., 2011a; Courchesne et al., 2011b; Courchesne and Pierce, 2005; Ecker et al., 2013; Zielinski et al., 2014). The brain undergoes a period of precocious growth in the early postnatal life of ASD individuals. This is followed by decreased or paused age-related brain growth, so that in later childhood and adolescence there are no differences in total brain volume compared to neurotypical individuals. Moreover, later on in adulthood and older age, there seems to be an acceleration in age-related brain degeneration. This theory has been supported by findings in longitudinal and cross-sectional MRI studies (Courchesne et al., 2011a; Courchesne et al., 2011b) While the early overgrowth found in volumetric MRI-studies of ASD pertains mostly to the frontal and temporal lobes (Amaral et al., 2008; Carper and Courchesne, 2005; Pagnozzi et al., 2018; Riddle et al., 2017), the abnormal age-related degeneration is also region-specific but focused more in the temporal and parietal lobes (Braden and Riecken, 2019; Wallace et al., 2010). MRI and post-mortem studies also support a similar abnormal growth trajectory in the cerebellum, but with the exception of life-long hypoplasia in the vermis areas (Amaral et al., 2008; Pagnozzi et al., 2018). The cerebellum has traditionally been viewed as related to motor functions, but recent studies have also demonstrated its role in social cognition (Moreno-Rius, 2019; Schmahmann, 2019; Van Overwalle et al., 2015).

1.2. Abnormalities in the frontotemporal, limbic, and cerebellar areas of psychopathy

Psychopathy is a serious disorder of social cognition characterized by grandiosity, callousness, manipulativeness, and lack of remorse, empathy, and guilt. It is often comorbid with conduct disorder and antisocial personality disorder (Johanson et al., 2020). Psychopathy is strongly associated with violence and criminal recidivism (Junewicz and Billick 2020) and is overrepresented in prisoner populations (Johanson et al., 2020). Several biological findings support the theories that conduct disorder in childhood and youth represent a neurodevelopmental precursor to antisocial personality disorder and psychopathy (Junewicz and Billick, 2020; Raine, 2018). Neuroimaging studies in psychopathy research have reported heterogenous results, but a recent systematic review established decreased grey matter volumes in frontotemporal, limbic, paralimbic, and cerebellar structures as the most evident neuroanatomical correlates of psychopathy (Johanson et al., 2020). A recent meta-analysis also showed decreased grey matter volumes in dorsolateral cortex and medial orbitofrontal cortex of men with psychopathy (De Brito et al., 2021). Similar consistent findings of reduced grey matter volume in the frontotemporal and limbic regions is also consistently found in adolescents with conduct problems and aggression (Fairchild et al., 2019). Moreover, these findings are also associated with psychopathic traits in healthy controls and violent offenders (Nummenmaa et al., 2021).

1.3. Similarities and differences in socioemotional processing in ASD and psychopathy

The co-occurrence of psychopathy in autism is possible but rare (Rogers et al., 2006). However, although the clinical profiles of ASD and psychopathy differ considerably, these two disorders also display numerous shared features. A lack of empathy is common in both disorders. However, impairments in the cognitive aspects of empathy are more pronounced in ASD whereas the emotional aspects are more pronounced in psychopathy (Blair, 2008; Lockwood et al., 2013; O'Nions et al., 2014). Both disorders are overrepresented in forensic settings, but despite the elevated risk of violence in psychopathy, there is no evidence supporting a higher risk of violence or offenses in ASD (Howlin, 2000; Im, 2016; Johanson et al., 2020; King and Murphy, 2014; Siponmaa et al., 2001). Both of these disorders have their origin in the early childhood and thus can be viewed as neurodevelopmental disorders (Raine, 2018). When ASD and psychopathy both have a significant hereditary component (Blonigen et al., 2005; Larsson et al., 2006; Tuvblad et al., 2016; Tuvblad et al., 2014; Woodbury-Smith and Scherer, 2018), they also share some of their genetic basis (O'Nions et al., 2015; Tick et al., 2016; Tiihonen et al., 2020).

Only a few imaging studies have compared the brain basis of these two disorders directly. In a study of 323 typically developing and normally functioning adolescents, higher psychopathic traits were associated with lower cortical thickness in the anterior prefrontal cortex and higher ASD traits were associated with lower cortical thickness in the superior temporal and temporoparietal regions. The only overlapping region of cortical thinning as a function of psychopathic and autistic traits was seen in the left medial parietal cortex (Wallace et al., 2012). One fMRI study using empathy tasks showed reduced responses of brain regions involved in cognitive empathy in youths with ASD; in turn, youths with conduct disorder and callous-unemotional traits showed reduced responses in brain regions involved in emotional empathy compared to typically developing individuals (Klapwijk et al., 2016). In a study using theory of mind tasks, the children with ASD showed atypical neural processing compared to typically developing children, but there was no difference between children with conduct problems and high callous-unemotional traits and typically developing children (O'Nions et al., 2014). In our recent fMRI study comparing these disorders in tasks of social cognition (emotion perception), we found reduced responses in the motor cortex areas of both of these disorders, suggesting an aberrant motor contagion of emotions (Sun et al., 2021).

1.4. The current study

The purpose of this study was to provide insight to investigate structural differences in ASD and criminal psychopathy. We used voxel-base morphometry (VBM) to compare the regional grey matter volume between participants belonging to either of these study groups as well as a group of controls. In a recent structural brain imaging study using the same psychopathic participants, the main findings were decreased grey matter volumes of the insula, the frontal cortex, and the sensorimotor cortex in violent offenders with psychopathic traits compared to control participants (Nummenmaa et al., 2021). Based on prior studies, we predicted lower grey matter volume (GMV) values in temporo-parietal and cerebellar areas of the ASD compared to control participants. In comparison with the previously studied violent offenders with high psychopathy traits, we predicted lower GMV values in the parietal social cognition areas of the ASD, while the offenders would in turn show lower values in frontal social cognition areas.

2. Materials and methods

2.1. Subjects

Twenty individuals with high functioning ASD (mean age 28 years, range 20–40 years), 19 convicted violent offenders (mean age 31 years, range 23–45 years), and 19 controls (mean age 29 years, range 21–47 years) participated in the study. All subjects gave informed, written consent and were compensated for their participation. The ethics board of the Hospital District of Southwest Finland approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. The study also obtained a research permit from the Hospital District of Helsinki and Uusimaa since the ASD group participants were largely recruited from this area.

The general inclusion criteria for all groups were male sex and age of 20–50 years. The general exclusion criteria for all groups were current use of narcotics, current abusive use of alcohol (over 14 U /week), severe axis I psychiatric illnesses, autoimmune illnesses, current medical conditions, and the standard MRI exclusion criteria.

Inclusion criterion for the ASD group was a valid autism spectrum disorder diagnosis, and inclusion criterion for the group of violent offenders with psychopathy traits was a current sentence for at least one violent crime (murder, manslaughter, rape, assault). Inclusion criteria for control group were a clean criminal record and no history of neurological or psychiatric disorders.

Offender group participants were inmates of Turku Prison who had been sentenced for murder ($n = 5$), manslaughter ($n = 5$), attempted manslaughter ($n = 3$), or grievous bodily harm ($n = 6$). They were each escorted by two prison guards to the local research institute for the brain imaging study. Psychiatric diagnoses of the offender group were based on prison health care and forensic psychiatric violence risk assessments, or most thorough forensic psychiatric examination reports concerning legal responsibility, two recruitment interviews, and semi-structured PCL-R interviews. Only two of the offenders refused to be evaluated with the PCL-R interview. In the Scandinavian countries the PCL-R cut-off limit for psychopathy has been suggested to be lower than the North American one and in the range of 25–26 (Jüriloo et al., 2014). Final consensus diagnoses were made by two medical specialists both in psychiatry and forensic psychiatry with 13–25 years of experience in the field of prison psychiatry, who were assisted by a psychologist with a 15-year working history in a Psychiatric Hospital for Prisoners. Possible opioid and dopaminergic medications were mostly withdrawn before the measurements, but it was not possible to execute a total discontinuation of the medications. Clinical information of offenders is found in supplement S1.

Subjects in the ASD group were volunteers from the Helsinki and Turku University Hospital Neuropsychiatric Clinics, with one subject also recruited from Neuropsychiatric Clinic Proneuron, in Espoo. The ASD group diagnoses were verified by a research psychologist, neurologist, and psychiatrist following DSM-5 criteria based on patient history, all accessible information from births records, well-baby clinics, and school healthcare. Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) assessment (Lord et al., 2012) was also used to clarify the autism diagnostics. Possible opioid and dopaminergic medications were withdrawn before measurements, but it was not possible to execute a total discontinuation of the medications. Clinical information of the ASD subjects is found in supplement S2.

The control participants were screened for medical conditions from their patient histories and their use of prescribed medication was double-checked from the Finnish medical database. Clinical information of the control subjects is found in supplement S3.

All the participants completed the Autism-Spectrum Quotient (AQ) questionnaire for the evaluation of ASD (Baron-Cohen et al., 2001; Bishop et al., 2004). AQ comprises 50 questions measuring five different areas of autism spectrum disorder: social skill, attention switching, attention to detail, communication, and imagination. As all the participants in control group scored below the 32 cut-off limit in the AQ, they were considered non-autistic and ADOS-2 evaluation was not considered necessary (Baron-Cohen et al., 2001). Three of the offender group did not complete the AQ questionnaire. One participant in the offender group scored 35 but showed no evidence of ASD in clinical evaluations and ADOS-2 evaluations in this group were also not considered necessary. Psychopathy was evaluated with Levenson Self-Report Psychopathy Scale (LSRP) questionnaire across all the participants (Levenson et al., 1995). LSRP measures two dimensions of psychopathy: primary psychopathy, indicating inclination to lie, lack of remorse, and callousness, and secondary psychopathy indicating impulsivity, short temper, and low tolerance for frustration. As all the participants in control and the ASD groups scored below 49 in the LSRP, they were considered non-psychopathic and PCL-R evaluation was not considered necessary (Brinkley et al., 2001). None of the participants had previous or current severe mental disorders, as assessed by SCID-I interview (Spitzer et al., 1992). The education of all the participants was classified in three different categories: (1) primary school, (2) secondary degree, (3) university degree. All the participants were also screened for their clinical status, with comprehensive general blood laboratory exams, including a urinary test for the use of narcotics. Subject characteristics can be found in Table 1A & B.

2.2. MR imaging and analysis

Structural MRI data were collected using a Phillips Ingenuity TF PET/MR 3 T scanner. We used a T1-weighted sequence (TR 9.8 ms, TE 4.6 ms, flip angle 7°, 250 mm FOV, 256 × 256 voxel matrix) with (1 mm^3) isotropic voxel size. The T1 images were screened for structural abnormalities by a radiologist. We used SPM12 (Wellcome Trust Center for Imaging, London, UK, https://www.fil.ion.ucl.ac.uk/spm) to conduct the voxel-based morphometry, applying automated spatial normalization, tissue classification, and radio-frequency bias correction combined with the segmentation step. Medium affine regularization 0.01 was used with a 25 mm cut-off for spatial normalization. Following normalization and segmentation into grey matter and white matter, we incorporated a non-linear transformation step, as implemented in CAT12 toolbox, to take into account volume changes caused by spatial

Table 1A
Subject characteristics.

	Controls Mean (SD)	ASD Mean (SD)	Offenders Mean (SD)
Age	29 (8)	28 (6)	31 (7)
n (males)	19	20	19
Education*			
No graduation	0	0	2
Primary School	0	3	11
Second degree	10	14	5
University	9	3	0
Psychopathy			
PCL-R	–	–	26 (5) $n = 17$
LSRP primary [1]	22 (3)	23 (4)	31 (6) $n = 15$
LSRP secondary*	13 (3)	17 (3)	20 (3) $n = 15$
Autism			
AQ*	11 (4)	28 (6)	20 (6) $n = 16$
ADOS-2	–	11 (4)	–
Handedness			
Right	16	13	16
Left	3	7	3

PCL-R = Psychopathy Checklist-Revisited, LSRP = Levenson Self-Report Psychopathy Scale, AQ = Autism Spectrum Quotient, ADOS-2 = Autism Diagnostic Observation Schedule-Second Edition.
*Significant $p < 0.05$ differences between all groups in ONE-WAY ANOVA analyses.
[1] Significant $p < 0.05$ differences between groups except between ASD and Healthy controls in ONE-WAY ANOVA analyses.

Table 1B
Subject characteristics.

	Controls Number of participants	ASD Number of participants	Offenders Number of participants
Current diagnoses:			
Autism Spectrum disorder	–	20	–
Antisocial personality disorder	–	–	16
Borderline personality disorder	–	–	4
ADHD	–	6	5
Previous diagnoses:			
Mood and Anxiety disorder	–	8	4
Substance abuse	–	–	18
Alcohol abuse	–	–	13
Medication:			
SSRIs, SNRIs	–	4	5
Tricyclic antidepressants	–	–	4
Other antidepressants	–	1	–
Hypnotics and Anxiolytics	–	3	6
Neuroleptics	–	–	6
Stimulants	–	2	1
Betablockers	–	–	2
Antihistamines	–	1	9
Levothyroxine	–	1	1

normalization. Similar non-linear transformation step was also used to account for the differences in total brain size across subjects. Finally, all the segmented, normalized, and modulated GM and WM images were smoothed using a Gaussian kernel of 8 mm full width at half maximum (FWHM).

In the full volume analysis, the normalized and smoothed VBM images were analyzed with SPM12 using General Linear Model. We first disclosed regional variations of grey matter volume among all groups using ANOVA F-tests, which was also used to find out group differences in the total intracranial volume and total grey matter volume. The further pair-wise comparisons between the groups were performed with T-tests of six different *t*-contrasts: 1) Offenders < ASD, 2) ASD < Controls, 3) Offenders < Controls, 4) ASD < Offenders, 5) Controls < ASD, 6) Controls < Offenders. The primary *p-value* threshold was set at < 0.01 with a cluster level extent threshold set at $q_{FDR\text{-}corr} < 0.05$. To pinpoint the most robust differences between groups, we also assessed the effects using stricter statistical thresholds (primary *p-value* thresholds at 0.005 and 0.001 with cluster level extent threshold set at $q_{FDR\text{-}corr} < 0.05$.). To better elucidate the between-groups differences, we also evaluated GMV in a priori regions of interest (ROI). The ROIs were set based on the previous anatomical imaging studies at frontal, temporal, insular and amygdala areas defined by the AAL atlas (Tzourio-Mazoyer et al., 2002) (supplement S4). As our earlier study showed fMRI differences in motor cortex function, we also evaluated an AAL-defined ROI at the precentral gyrus for any anatomical differences between these groups (Sun et al., 2021). In addition to the group comparisons, we conducted continuous analyses based on the LSRP and AQ questionnaire scores.

3. Results

3.1. Voxel-based morphometry

ANOVA (F-test) analyses revealed significant group differences in the right temporal pole, left fusiform cortex, left insular cortex, right culmen of vermis, left frontal pole, left inferior frontal gyrus, cingulate gyrus, left precuneus, and right precentral gyrus, with FDR-thresholded at $p < 0.01$. In the pair-wise comparisons the offenders versus ASD group, GMV was lower in the right temporal pole and left inferior frontal gyrus (Fig. 1A). These findings were still significant when the *p*-threshold was tightened all the way from 0.01 to 0.001 (supplement S5). AQ and LSRP scores had no correlation with GMV in any of these areas. In the ASD versus control group, GMV was lower in the right precentral cortex, left precuneus, right culmen of vermis, and the right cerebellum areas (Fig. 1B). These findings were still significant when the *p*-threshold was tightened from 0.01 to 0.001 (supplement S5). The AQ scores had a negative correlation with GMV in all of these areas, with an FDR threshold at $p < 0.01$. In the offender versus control group, GMV was found to be lower in the bilateral insular cortex, left frontal pole, right precentral cortex, cingulate gyrus, left inferior temporal gyrus, and left fusiform cortex (Fig. 1C). These findings were still significant when the *p*-threshold was tightened from 0.01 to 0.001 (supplement S5). The total LSRP and primary psychopathy domain scores had a negative correlation with GMV (FDR corrected at $p < 0.01$) only in the left frontal pole. Secondary psychopathy domain was not associated with GMV using the same threshold. There was an overlapping region in the precentral cortex where both offender and ASD groups showed lower GMV in comparison with controls (Fig. 2). When education, total intracranial volume, and age were used as covariates, the results remained essentially unchanged (FDR corrected, $p < 0.01$). We also found no differences in the total intracranial volume ($p = 0.1553$) and total grey matter volume ($p = 0.0732$) in ANOVA analyses. No significant voxels were found in the opposite contrasts (Offender > ASD, ASD > Controls, and Offender > Control). Stereotactic coordinates and *t*-values for the results can be found in supplement S4.

3.2. ROI analyses

The ROI analyses of the temporal areas showed lower GMV in the right temporal inferior, right middle temporal pole, and left temporal pole superior regions of the offenders versus ASD group. In frontal areas, only the left frontal inferior triangular region of the offender group showed significantly lower GMV compared to the ASD group (Fig. 3). In the ASD group, only the precentral region showed lower GMV compared to controls, with no significant difference in the temporal, frontal or insular areas (Fig. 3). The offender group had significantly lower GMV of the bilateral temporal inferior, right temporal pole, left middle temporal pole, and right temporal pole superior regions compared with the control group. In the frontal areas, the offender group had lower GMV of the left frontal inferior operculum, left frontal inferior triangular, bilateral middle orbital, left frontal superior orbital, left frontal inferior orbital, left frontal medial orbital, left frontal middle, and bilateral frontal superior medial regions. There was also lower GMV in bilateral insula and right precentral gyrus regions of the offenders compared to control group (Fig. 3). The amygdala area did not show any significant differences between groups. Statisics for regional tests are shown in supplement S6.

4. Discussion

Our main finding was that violent offenders with psychopathic traits have lower GMV in frontotemporal areas associated with social cognition when compared with ASD individuals, but compared to controls, both individuals with ASD and psychopathy present similar lower GMV in motor areas. In comparison with controls, the offender group had widespread lower grey matter volume in frontotemporal areas, while the ASD group showed lower volume in the precuneus and cerebellum. In addition to these divergent patterns, both ASD and offender groups had lower grey matter volume in the pre-central motor cortex when compared to the control group. Altogether these results suggest that ASD and psychopathy involve distinct patterns of structural alterations in the brain, the commonalities and shared patterns of lowered GMV may

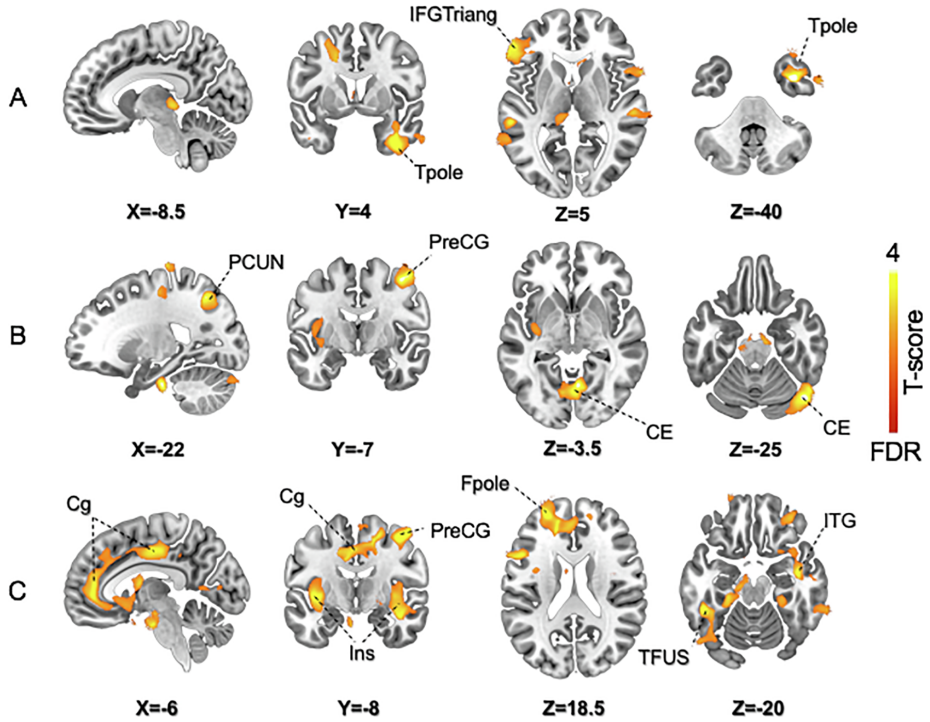


Fig. 1. A. Brain regions with lower GMV in offender versus ASD group. The data FDR-thresholded at $p < 0.01$. Tpole = Temporal pole, IFGtriang = Inferior Frontal Gyrus, Triangular part B. Brain regions with lower GMV in ASD versus Controls. The data is FDR-thresholded at $p < 0.01$ PreCG = Precentral Gyrus, PCUN = Precuneus, CE = Cerebellum C. Brain regions with lower GMV in Offenders vs Controls. The data are FDR-thresholded at $p < 0.01$ PreCG = Precentral Gyrus, Fpole = Frontal pole, INS = Insula, Cg = Cingulate Gyrus, ITG = Inferior Temporal Gyrus, TFUS = Temporal Fusiform Gyrus.

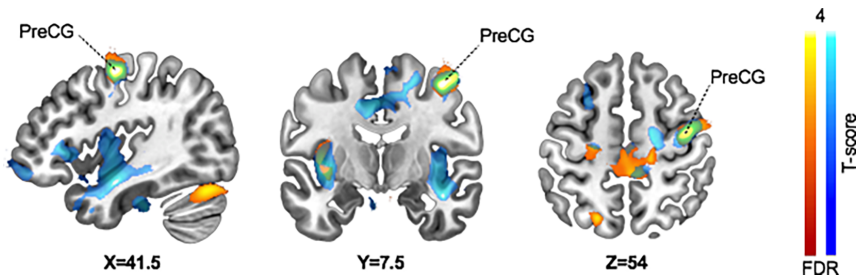


Fig. 2. Overlapping (green) brain regions with lower grey matter volume in ASD (red) and Offender groups (blue) compared to control group. The data are FDR-thresholded at $p < 0.01$. *PreCG = Precentral Gyrus.*.

explain some of the shared phenotypical features of these groups. The ANOVA analyses revealed GMV differences in similar areas as found in the pair-wise T-test comparisons; the only exceptions were additional effects in the right cerebellar and right insular areas.

4.1. Lower grey matter volume values in the frontotemporal areas of violent offenders with psychopathy traits compared to autism spectrum disorder individuals

When comparing the offenders and ASD groups, we found significantly lower GMV values in the right temporal pole and left frontal inferior triangular gyrus of the offenders. The differences were robust and significant with a primary threshold of 0.001. Both of these areas are associated with social cognition and related to emotional aspects of empathy (Leigh et al., 2013; Sato and Uono, 2019). In the ROI analyses we also found lower GMV values for the offenders versus ASD group in regions involved in social cognition (superior temporal pole, middle and inferior temporal pole, and inferior triangular gyrus). In ASD the frontotemporal areas are impaired by overgrowth in childhood and accelerated degeneration in adulthood and older age (Courchesne et al.,

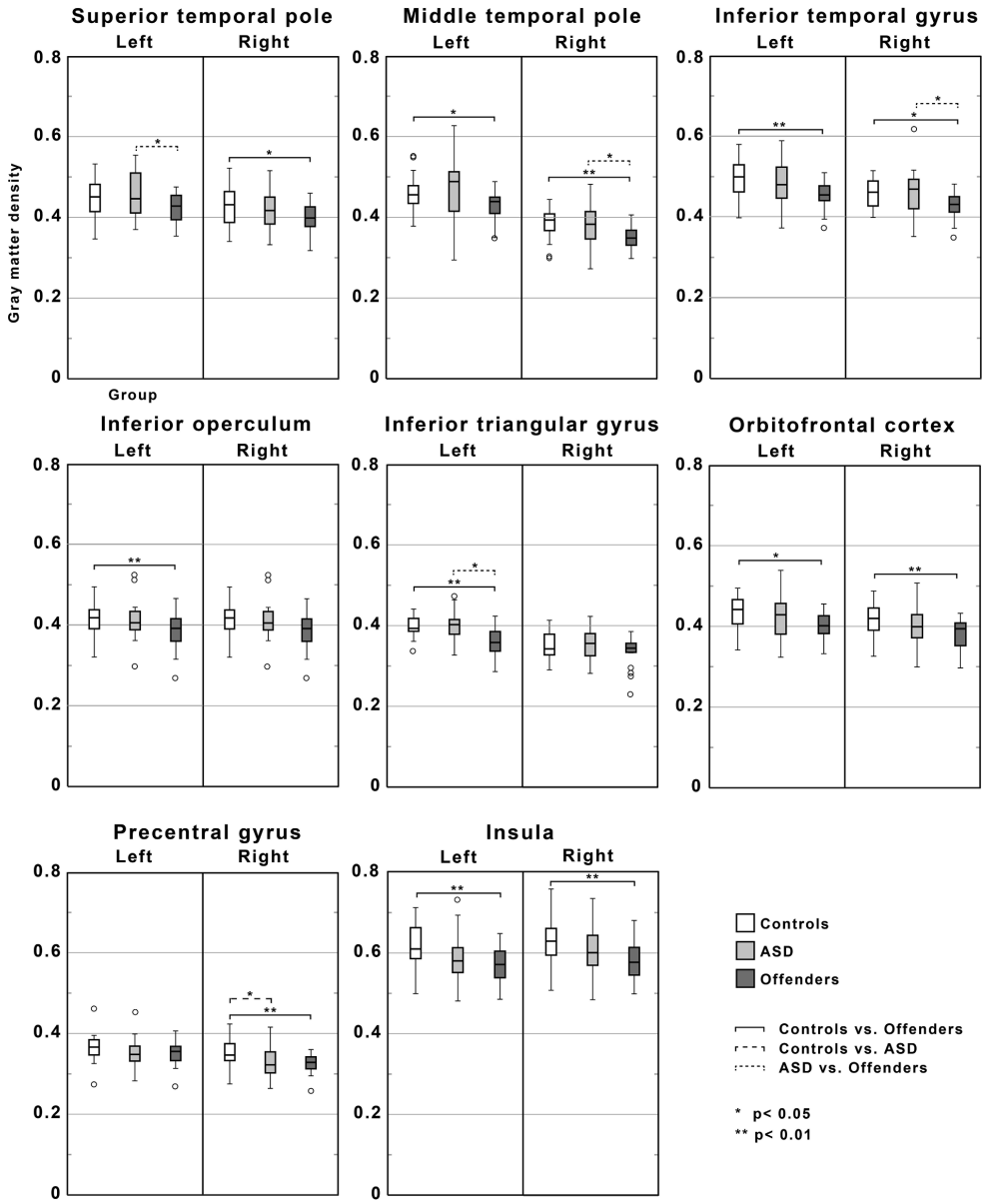


Fig. 3. Regional GMV in frontal, temporal, insular and precentral regions of interest (ROI) across the three groups. Asterisks denote statistically significant differences between groups.

2011a; Courchesne et al., 2011b; Zielinski et al., 2014). In psychopathy, these frontotemporal areas are already seen to be affected at neurodevelopmental precursor stages of childhood and subsequently throughout adulthood (Fairchild et al., 2019; Johanson et al., 2020; Rogers and De Brito, 2016). Along with these divergent growth trajectories, our findings suggest different pathological mechanisms behind the frontotemporal defects in these disorders, but this needs further research.

4.2. Similar lower grey matter volume areas in the motor cortex of violent offenders with psychopathy traits and autism spectrum disorder individuals

The full-volume analysis revealed lower GMV in right precentral cortex of both offender and ASD groups compared with the controls. Importantly, GMV in this region did not differ between these two groups (ASD and Offenders). This effect was also confirmed in the ROI analyses. Aberrant structure of this precentral area might suggest a similar

impairment of motor functioning in both groups. Deficits in motor areas are consistently found in ASD (Fournier et al., 2010a; Mosconi and Sweeney, 2015; Nebel et al., 2014), but there is also evidence of functional and anatomical deviancies of motor cortex in psychopathy (De Brito et al., 2021; Robinson and Bresin, 2014; Tillem et al., 2019). Similarly as mentioned before, there is evidence of abnormal growth trajectory of the ASD also in the motor cortex regions (Mostofsky et al., 2007; Riddle et al., 2017). As our ASD participants were all adults, our findings could reflect this abnormal age-related degeneration of the motor cortex. The functional organization of the motor cortex is also disrupted in children with ASD (Nebel et al., 2012), and significant and widespread alterations in motor performance have even been argued to precede the core symptoms of ASD (Fournier et al., 2010b; Mosconi and Sweeney, 2015). There are also reports of increased motor and premotor cortex white matter volumes positively correlating with poor motor function in ASD (Mostofsky et al., 2007). A study of ASD individuals in a high security prison has also interestingly shown a positive correlation between motor clumsiness and antisocial lifestyle in PCL-R evaluations (Murphy, 2007). To our knowledge, there is only one study that has observed decreased grey matter values in the motor cortex of children with conduct problems and aggression (Fairchild et al., 2019). Slightly similar overlapping findings have earlier been seen in the cortical thickness of psychopathy and ASD traits compared to healthy controls but these were located more in the parietal cortex (Wallace et al., 2012). In our latest fMRI study with the same participants, we found uniting altered somatosensory and motor responses to emotional expressions in the ASD and offender group, reflecting functional problems in these same brain areas (Sun et al., 2021). Here our anatomical findings also suggest similar aberrancies in the motor areas in these two groups. Along with motor functioning problems, these findings could also be possibly related to issues of social cognition such as motor imagination, motor observation, and motor empathy (Bhattacharjee et al., 2021; Bons et al., 2013).

4.3. Lower grey matter volume values in ASD compared to controls

In the ASD group we found lower grey matter volume values in the right cerebellum, left precuneus, and right pre-motor cortex compared to controls. Comparable areas also had a negative correlation with AQ scores. The lower grey matter values of the cerebellum in the ASD group is a consistent and can be seen as reflecting deficits in motor control but also social cognition in the ASD group (Moreno-Rius, 2019; Schmahmann, 2019; Van Overwalle et al., 2015). The precuneus is a part of the social cognition network and is interestingly linked with default-mode networks and sensing of self and others, which may be seen as reflecting deficits in the theory of mind of the ASD group (Cavanna and Trimble, 2006). All in all, the differences in the grey matter volume of social cognition areas in the ASD group were surprisingly small when compared to controls. This may be due to the phenotypical and genetic heterogeneity of the disorder and our relatively small sample size (Pelphrey et al., 2011).

4.4. Lower grey matter volume values in violent offenders with psychopathy traits compared to healthy controls

In an earlier study with the same offender and control participants, the main findings were lower grey matter volumes in the anterior insula, frontal cortex, and the sensorimotor areas in the violent offenders compared to controls (Nummenmaa et al., 2021). Consistent with this, we found lower grey matter values in the bilateral insular cortex, left frontal pole, right precentral cortex, cingulate gyrus, left inferior temporal gyrus, and left fusiform cortex in the offender group compared to the control group. The total and primary psychopathy domain scores of the LSRP questionnaire correlated negatively with the left frontal pole area. All the results are comparable with earlier findings from systematic reviews of psychopathy (De Brito et al., 2021; Johanson et al., 2020). The whole brain findings in this group were also robust and still clear with a p-value threshold of 0.001. In the ROI analyses the offender group also showed vastly lower GMV values in the frontal, temporal, and insular areas as well as the precentral cortex areas.

4.5. Limitations

The groups were matched by their age and sex, but there were statistically significant differences in education between groups. Although controlling for education in the statistical analysis did not essentially change the results, we recommend formal IQ evaluations in future studies with similar comparison setups. Also, since we only included male subjects, our findings may not be generalized to females. Although there was no evidence of current alcohol or drug abuse in any participants as a confounding factor, the history of abuse in the offender group was still more common. The MR images and patient histories of our subjects did not indicate any brain injuries, but these might nevertheless be more common in violent offenders (Katzin et al., 2020). Since the screening questionnaires raised a justified suspicion of co-occurrent psychopathy and ASD in one of our participants (Rogers et al., 2006), we recommend more diagnostic ADOS-2 and PCL-R evaluations across all groups in future studies with similar comparison setups. Finally, the sample size was limited due to the complicated recruitment and measurement protocols in the prison environment. However, we used strict statistical significance and were nevertheless able to establish consistent differences between the groups.

4.6. Conclusion

We conclude that lower grey matter volume of the right temporal pole and left inferior frontal gyrus in violent offenders with high psychopathy traits is the most salient structural difference in comparison with ASD individuals. These brain areas have been linked with both psychopathy (Johanson et al., 2020) and ASD in previous studies of these social cognition deficits (Courchesne et al., 2011a; Courchesne et al., 2011b). Interestingly, these areas are linked with emotional aspects of empathy, which is seen as more defective in psychopathy (Blair, 2008; Fitzgerald, 2019; Jones et al., 2010; Lockwood et al., 2013). The ASD group showed surprisingly little grey matter loss in any of the areas typically associated with social cognition, possibly due to the phenotypical and genetical heterogeneity of the disorder. We also found decreased grey matter volume values in similar areas of the right precentral cortex in both groups. As motor function impairment is a well-known early onset deficit in the ASD group, there is only little knowledge of this issue on the psychopathy trait. Considering the nature of these disorders, the motor cortex finding could possibly be also more closely related to similar issues of social cognition such as motor imagination, motor observation, and motor empathy.

Declaration of competing interest

Jari Tiihonen has participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to his employing institution, and has - been a consultant and/or advisor to and/or has received honoraria from: Eli Lilly, Evidera, Janssen-Cilag, Lundbeck, Orion, Otsuka, Mediuutiset, Sidera, and Sunovion.

CRediT authorship contribution statement

Tuomo Noppari: Formal analysis, Investigation, Writing – original draft, Visualization. **Lihua Sun:** Software, Formal analysis, Investigation, Data curation, Writing – review & editing. **Lasse Lukkarinen:** Formal analysis, Investigation. **Vesa Putkinen:** Software, Formal analysis, Investigation, Data curation, Writing – review & editing. **Pekka Tani:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision. **Nina Lindberg:** Resources, Writing – review &

editing, Funding acquisition. **Emma Saure:** Investigation, Writing – review & editing. **Hannu Lauerma:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision. **Jari Tiihonen:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision. **Niina Venetjoki:** Investigation, Resources, Writing – review & editing. **Marja Salomaa:** Investigation, Resources, Writing – review & editing. **Päivi Rautio:** Investigation, Resources. **Jussi Hirvonen:** Investigation, Resources. **Juha Salmi:** Conceptualization, Software, Validation, Resources, Writing – review & editing, Visualization, Supervision. **Lauri Nummenmaa:** Conceptualization, Methodology, Software, Validation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The study was supported by the Academy of Finland (grants numbers 294897 and 332225, to L.N.), Valon Vuoksi Foundation (grants to L.S. and L.L.) and Turku Collegium for Science and Medicine, University of Turku (to L.S.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103116.

References

Amaral, D.G., Schumann, C.M., Nordahl, C.W., 2008. Neuroanatomy of autism. Trends Neurosci. 31, 137–145. https://doi.org/10.1016/j.tins.2007.12.005.

Amodio, D.M., Frith, C.D., 2006. Meeting of minds: the medial frontal cortex and social cognition. Nat. Rev. Neurosci. 7, 268–277. https://doi.org/10.1038/nrn1884.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E., 2001. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Malesand Females, Scientists and Mathematicians. J. Autism Dev. Disord. 31, 5–17. https://doi.org/10.1023/A:1005653411471.

Bhattacharjee, S., Kashyap, R., Abualait, T., Annabel Chen, S.-H., Yoo, W.-K., Bashir, S., 2021. The Role of Primary Motor Cortex: More Than Movement Execution. J. Mot. Behav. 53, 258–274. https://doi.org/10.1080/00222895.2020.1738992.

Bishop, D.V.M., Maybery, M., Maley, A., Wong, D., Hill, W., Hallmayer, J., 2004. Using self-report to identify the broad phenotype in parents of children with autistic spectrum disorders: A study using the Autism-Spectrum Quotient. J. Child Psychol. Psychiatry. 45 (8), 1431–1436. https://doi.org/10.1111/j.1469-7610.2004.00325.x.

Blair, R.J.R., 2008. Fine cuts of empathy and the amygdala: dissociable deficits in psychopathy and autism. Q. J. Exp. Psychol. 2006 (61), 157–170. https://doi.org/10.1080/17470210701508855.

Blakemore, S.-J., 2012. Development of the social brain in adolescence. J. R. Soc. Med. 105, 111–116. https://doi.org/10.1258/jrsm.2011.110221.

Blonigen, D.M., Hicks, B.M., Krueger, R.F., Patrick, C.J., Iacono, W.G., 2005. Psychopathic personality traits: heritability and genetic overlap with internalizing and externalizing psychopathology. Psychol. Med. 35, 637–648. https://doi.org/10.1017/S0033291704004180.

Bons, D., van den Broek, E., Scheepers, F., Herpers, P., Rommelse, N., Buitelaaar, J.K., 2013. Motor, Emotional, and Cognitive Empathy in Children and Adolescents with Autism Spectrum Disorder and Conduct Disorder. J. Abnorm. Child Psychol. 41, 425–443. https://doi.org/10.1007/s10802-012-9689-5.

Braden, B.B., Riecken, C., 2019. Thinning faster? Age-related cortical thickness differences in adults with autism spectrum disorder. Res. Autism Spectr. Disord. 64, 31–38. https://doi.org/10.1016/j.rasd.2019.03.005.

Brinkley, C.A., Schmitt, W.A., Smith, S.S., Newman, J.P., 2001. Construct validation of a self-report psychopathy scale: does Levenson's self-report psychopathy scale measure the same constructs as Hare's psychopathy checklist-revised? Personal. Individ. Differ. 31, 1021–1038. https://doi.org/10.1016/S0191-8869(00)00178-1.

Carper, R.A., Courchesne, E., 2005. Localized enlargement of the frontal cortex in early autism. Biol. Psychiatry 57, 126–133. https://doi.org/10.1016/j.biopsych.2004.11.005.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain J. Neurol. 129, 564–583. https://doi.org/10.1093/brain/awl004.

Courchesne, E., Campbell, K., Solso, S., 2011a. Brain growth across the life span in autism: age-specific changes in anatomical pathology. Brain Res. 1380, 138–145. https://doi.org/10.1016/j.brainres.2010.09.101.

Courchesne, E., Karns, C., Davis, H., Ziccardi, R., Carper, R., Tigue, Z., Chisum, H.J., Moses, P., Pierce, K., Lord, C., Lincoln, A., Pizzo, S., Schreibman, L., Haas, R., Akshoomoff, N., Courchesne, R., 2011b. Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. Neurology 76. https://doi.org/10.1212/01.wnl.0000399191.79091.28.

Courchesne, E., Pierce, K., 2005. Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. Int. J. Dev. Neurosci. 23, 153–170. https://doi.org/10.1016/j.ijdevneu.2005.01.003.

Courchesne, E., Pierce, K., Schumann, C.M., Redcay, E., Buckwalter, J.A., Kennedy, D.P., Morgan, J., 2007. Mapping Early Brain Development in Autism. Neuron 56, 399–413. https://doi.org/10.1016/j.neuron.2007.10.016.

De Brito, S.A., McDonald, D., Camilleri, J.A., Rogers, J.C., 2021. Cortical and subcortical gray matter volume in psychopathy: A voxel-wise meta-analysis. J. Abnorm. Psychol. 130, 627–640. https://doi.org/10.1037/abn0000698.

Ecker, C., Spooren, W., Murphy, D.G.M., 2013. Translational approaches to the biology of Autism: false dawn or a new era? Mol. Psychiatry 18, 435–442. https://doi.org/10.1038/mp.2012.102.

Fairchild, G., Hawes, D.J., Frick, P.J., Copeland, W.E., Odgers, C.L., Franke, B., Freitag, C.M., De Brito, S.A., 2019. Conduct disorder. Conduct disorder primer. 5 (1) https://doi.org/10.1038/s41572-019-0095-y.

Fernández, M., Mollinedo-Gajate, I., Peñagarikano, O., 2018. Neural Circuits for Social Cognition: Implications for Autism. Neuroscience 370, 148–162. https://doi.org/10.1016/j.neuroscience.2017.07.013.

Fitzgerald, M., 2019. Empathy: Autism and Psychopathy. In: Kondo, M., Nikku, B. (Eds.), Empathy Study. IntechOpen.

Fournier, K.A., Hass, C.J., Naik, S.K., Lodha, N., Cauraugh, J.H., 2010. Motor Coordination in Autism Spectrum Disorders: A Synthesis and Meta-Analysis. J. Autism Dev. Disord. 40, 1227–1240. https://doi.org/10.1007/s10803-010-0981-3.

Howlin, P., 2000. Outcome in Adult Life for more Able Individuals with Autism or Asperger Syndrome. Autism 4, 63–83. https://doi.org/10.1177/1362361300004001005.

Im, D.S., 2016. Template to Perpetrate: An Update on Violence in Autism Spectrum Disorder. Harv. Rev. Psychiatry 24, 14–35. https://doi.org/10.1097/HRP.0000000000000087.

Johanson, M., Vaurio, O., Tiihonen, J., Lähteenvuo, M., 2020. A Systematic Literature Review of Neuroimaging of Psychopathic Traits. Front. Psychiatry 10. https://doi.org/10.3389/fpsyt.2019.01027.

Jones, A.P., Happé, F.G.E., Gilbert, F., Burnett, S., Viding, E., 2010. Feeling, caring, knowing: different types of empathy deficit in boys with psychopathic tendencies and autism spectrum disorder. J. Child Psychol. Psychiatry 51, 1188–1197. https://doi.org/10.1111/j.1469-7610.2010.02280.x.

Junewicz, A., Billick, S.B., 2020. Conduct Disorder: Biology and Developmental Trajectories. Psychiatr. Q. 91, 77–90. https://doi.org/10.1007/s11126-019-09678-5.

Jüriloo, A., Lauerma, H., Holmalahti, T., Tyni, S., Aarnio, J., Viitanen, P., Wuolijoki, T., Mattila, A., Lintonen, T., Joukamaa, M., Vartiainen, H., 2014. Psychopathic traits in a representative sample of Finnish male prisoners. Nord J Psychiatry. 68, 117–122. https://doi.org/10.3109/08039488.2013.780259.

Katzin, S., Andiné, P., Hofvander, B., Billstedt, E., Wallinius, M., 2020. Exploring Traumatic Brain Injuries and Aggressive Antisocial Behaviors in Young Male Violent Offenders. Front. Psychiatry 11, 507196. https://doi.org/10.3389/fpsyt.2020.507196.

King, C., Murphy, G.H., 2014. A Systematic Review of People with Autism Spectrum Disorder and the Criminal Justice System. J. Autism Dev. Disord. 44, 2717–2733. https://doi.org/10.1007/s10803-014-2046-5.

Klapwijk, E.T., Aghajani, M., Colins, O.F., Marijnissen, G.M., Popma, A., van Lang, N.D. J., van der Wee, N.J.A., Vermeiren, R.R.J.M., 2016. Different brain responses during empathy in autism spectrum disorders versus conduct disorder and callous-unemotional traits. J. Child Psychol. Psychiatry 57, 737–747. https://doi.org/10.1111/jcpp.12498.

Lahnakoski, J., Glerean, E., Salmi, J., Jääskeläinen, I., Sams, M., Hari, R., Nummenmaa, L., 2012. Naturalistic fMRI Mapping Reveals Superior Temporal Sulcus as the Hub for the Distributed Brain Network for Social Perception. Front. Hum. Neurosci. 6, 233. https://doi.org/10.3389/fnhum.2012.00233.

Larsson, H., Andershed, H., Lichtenstein, P., 2006. A genetic factor explains most of the variation in the psychopathic personality. J. Abnorm. Psychol. 115, 221–230. https://doi.org/10.1037/0021-843X.115.2.221.

Leigh, R., Oishi, K., Hsu, J., Lindquist, M., Gottesman, R.F., Jarso, S., Crainiceanu, C., Mori, S., Hillis, A.E., 2013. Acute lesions that impair affective empathy. Brain 136, 2539–2549. https://doi.org/10.1093/brain/awt177.

Levenson, M.R., Kiehl, K.A., Fitzpatrick, C.M., 1995. Assessing Psychopathic Attributes in a Noninstitutionalized Population. J. Pers. Soc. Psychol. 68 (1), 151–158. https://doi.org/10.1037/0022-3514.68.1.151.

Lockwood, P.L., Bird, G., Bridge, M., Viding, E., 2013. Dissecting empathy: high levels of psychopathic and autistic traits are characterized by difficulties in different social information processing domains. Front. Hum. Neurosci. 7, 760. https://doi.org/10.3389/fnhum.2013.00760.

Lord, C., Rutter, M., DiLavore, P., Risi, S., Gotham, K., Bishop, S., 2012. Autism Diagnostic Observation Schedule, (ADOS-2) Modules 1–4. Los Angeles, California.

Moreno-Rius, J., 2019. Is there an "antisocial" cerebellum? Evidence from disorders other than autism characterized by abnormal social behaviours. Prog.

Neuropsychopharmacol. Biol. Psychiatry 89, 1–8. https://doi.org/10.1016/j.pnpbp.2018.08.025.
Mosconi, M.W., Sweeney, J.A., 2015. Sensorimotor dysfunctions as primary features of autism spectrum disorders. Sci. China Life Sci. 58 (10), 1016–1023.
Mostofsky, S.H., Burgess, M.P., Gidley Larson, J.C., 2007. Increased motor cortex white matter volume predicts motor impairment in autism. Brain 130, 2117–2122. https://doi.org/10.1093/brain/awm129.
Murphy, D., 2007. Hare Psychopathy Checklist Revised profiles of male patients with Asperge's syndrome detained in high security psychiatric care. J. Forensic Psychiatry Psychol. 18, 120–126. https://doi.org/10.1080/14789940601014777.
Nebel, M.B., Joel, S.E., Muschelli, J., Barber, A.D., Caffo, B.S., Pekar, J.J., Mostofsky, S. H., 2012. Disruption of functional organization within the primary motor cortex in children with autism. Hum. Brain Mapp. 35, 567–580. https://doi.org/10.1002/hbm.22188.
Nebel, M.B., Eloyan, A., Barber, A.D., Mostofsky, S.H., 2014. Precentral gyrus functional connectivity signatures of autism. Front. Syst. Neurosci. 8, 80. https://doi.org/10.3389/fnsys.2014.00080.
Nummenmaa, L., Calder, A.J., 2009. Neural mechanisms of social attention. Trends Cogn. Sci. 13, 135–143. https://doi.org/10.1016/j.tics.2008.12.006.
Nummenmaa, L., Lukkarinen, L., Sun, L., Putkinen, V., Seppälä, K., Karjalainen, T., Karlsson, H.K., Hudson, M., Venetjoki, N., Salomaa, M., Rautio, P., Hirvonen, J., Lauerma, H., Tiihonen, J., 2021. Brain Basis of Psychopathy in Criminal Offenders and General Population. Cereb. Cortex bhab072. 31 (9), 4104–4114. https://doi.org/10.1093/cercor/bhab072.
O'Nions, E., Tick, B., Rijsdijk, F., Happé, F., Plomin, R., Ronald, A., Viding, E., Jones, A., 2015. Examining the Genetic and Environmental Associations between Autistic Social and Communication Deficits and Psychopathic Callous-Unemotional Traits. PLoS ONE 10 (9), e0134331. https://doi.org/10.1371/journal.pone.0134331.
O'Nions, E., Sebastian, C.L., McCrory, E., Chantiluke, K., Happé, F., Viding, E., 2014. Neural bases of Theory of Mind in children with autism spectrum disorders and children with conduct problems and callous-unemotional traits. Dev. Sci. 17 (5), 786–796. https://doi.org/10.1111/desc.12167.
Pagnozzi, A.M., Conti, E., Calderoni, S., Fripp, J., Rose, S.E., 2018. A systematic review of structural MRI biomarkers in autism spectrum disorder: A machine learning perspective. Int. J. Dev. Neurosci. Off. J. Int. Soc. Dev. Neurosci. 71, 68–82. https://doi.org/10.1016/j.ijdevneu.2018.08.010.
Pelphrey, K.A., Shultz, S., Hudac, C.M., Wyk, B.C.V., 2011. Constraining Heterogeneity: The Social Brain and its Development in Autism Spectrum Disorder. J. Child Psychol. Psychiatry 52, 631–644. https://doi.org/10.1111/j.1469-7610.2010.02349.x.
Raine, A., 2018. Antisocial Personality as a Neurodevelopmental Disorder. Annu. Rev. Clin. Psychol. 14, 259–289. https://doi.org/10.1146/annurev-clinpsy-050817-084819.
Riddle, K., Cascio, C.J., Woodward, N.D., 2017. Brain structure in autism: a voxel-based morphometry analysis of the Autism Brain Imaging Database Exchange (ABIDE). Brain Imaging Behav. 11, 541–551. https://doi.org/10.1007/s11682-016-9534-5.
Robinson, M.D., Bresin, K., 2014. Higher Levels of Psychopathy Predict Poorer Motor Control: Implications for Understanding the Psychopathy Construct. J. Psychopathol. Behav. Assess. 36, 201–210. https://doi.org/10.1007/s10862-013-9388-8.
Rogers, J.C., De Brito, S.A., 2016. Cortical and Subcortical Gray Matter Volume in Youths With Conduct Problems: A Meta-analysis. JAMA Psychiatry 73, 64–72. https://doi.org/10.1001/jamapsychiatry.2015.2423.
Rogers, J., Viding, E., James Blair, R., Frith, U., Happé, F., 2006. Autism spectrum disorder and psychopathy: shared cognitive underpinnings or double hit? Psychol. Med. 36, 1789–1798. https://doi.org/10.1017/S0033291706008853.
Sato, W., Uono, S., 2019. The atypical social brain network in autism: advances in structural and functional MRI studies. Curr. Opin. Neurol. 32, 617–621. https://doi.org/10.1097/WCO.0000000000000713.
Schmahmann, J.D., 2019. The cerebellum and cognition. Neurosci. Lett. 688, 62–75. https://doi.org/10.1016/j.neulet.2018.07.005.
Siponmaa, L., Kristiansson, M., Jonson, C., Nydén, A., Gillberg, C., 2001. Juvenile and young adult mentally disordered offenders: the role of child neuropsychiatric disorders. J. Am. Acad. Psychiatry Law 29, 420–426.
Spitzer, R.L., Williams, J.B.W., Gibbon, M., First, M.B., 1992. The Structured Clinical Interview for DSM-III-R (SCID): I: History, Rationale, and Description. Arch. Gen. Psychiatry. https://doi.org/10.1001/archpsyc.1992.01820080032005.
Sun, L., Lukkarinen, L., Noppari, T., Nazari-Farsani, S., Putkinen, V., Seppälä, K., Hudson, M., Tani, P., Lindberg, N., Karlsson, H.K., Hirvonen, J., Salomaa, M., M, N.V., Lauerma, H., Tiihonen, J., Nummenmaa, L., 2021. Aberrant motor contagion of emotions in psychopathy and high-functioning autism. https://doi.org/10.1101/2021.07.05.450842.
Tick, B., Bolton, P., Happé, F., Rutter, M., Rijsdijk, F., 2016. Heritability of autism spectrum disorders: a meta-analysis of twin studies. J. Child Psychol. Psychiatry 57, 585–595. https://doi.org/10.1111/jcpp.12499.
Tiihonen, J., Koskuvi, M., Lähteenvuo, M., Virtanen, P.L.J., Ojansuu, I., Vaurio, O., Gao, Y., Hyötyläinen, I., Puttonen, K.A., Repo-Tiihonen, E., Paunio, T., Rautiainen, M.-R., Tyni, S., Koistinaho, J., Lehtonen, Š., 2020. Neurobiological roots of psychopathy. Mol. Psychiatry 25, 3432–3441. https://doi.org/10.1038/s41380-019-0488-z.
Tillem, S., Brennan, G., Wu, J., Mayes, L., Baskin-Sommers, A., 2019. Alpha response reveals attention abnormalities in psychopathy. Personal. Disord. Theory Res. Treat. 10, 291–296. https://doi.org/10.1037/per0000314.
Tuvblad, C., Bezdjian, S., Raine, A., Baker, L.A., 2014. The Heritability of Psychopathic Personality in 14 to 15 year Old Twins: A Multi-Rater, Multi-Measure Approach. Psychol. Assess. 26, 704–716. https://doi.org/10.1037/a0036711.
Tuvblad, C., Wang, P., Bezdjian, S., Raine, A., Baker, L.A., 2016. Psychopathic personality development from ages 9 to 18: Genes and environment. Dev. Psychopathol. 28, 27–44. https://doi.org/10.1017/S0954579415000267.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. NeuroImage 15, 273–289. https://doi.org/10.1006/nimg.2001.0978.
Van Overwalle, F., D'aes, T., Mariën, P., 2015. Social cognition and the cerebellum: A meta-analytic connectivity analysis. Hum. Brain Mapp. 36, 5137–5154. https://doi.org/10.1002/hbm.23002.
Wallace, G.L., Dankner, N., Kenworthy, L., Giedd, J.N., Martin, A., 2010. Age-related temporal and parietal cortical thinning in autism spectrum disorders. Brain 133, 3745–3754. https://doi.org/10.1093/brain/awq279.
Wallace, G.L., Shaw, P., Lee, N.R., Clasen, L.S., Raznahan, A., Lenroot, R.K., Martin, A., Giedd, J.N., 2012. Distinct Cortical Correlates of Autistic versus Antisocial Traits in a Longitudinal Sample of Typically Developing Youth. J. Neurosci. 32, 4856–4860. https://doi.org/10.1523/JNEUROSCI.6214-11.2012.
Woodbury-Smith, M., Scherer, S.W., 2018. Progress in the genetics of autism spectrum disorder. Dev. Med. Child Neurol. 60, 445–451. https://doi.org/10.1111/dmcn.13717.
Zielinski, B.A., Prigge, M.B.D., Nielsen, J.A., Froehlich, A.L., Abildskov, T.J., Anderson, J. S., Fletcher, P.T., Zygmunt, K.M., Travers, B.G., Lange, N., Alexander, A.L., Bigler, E. D., Lainhart, J.E., 2014. Longitudinal changes in cortical thickness in autism and typical development. Brain J. Neurol. 137, 1799–1812. https://doi.org/10.1093/brain/awu083.

II

Cerebral Cortex, 2023, **33**, 374–384
https://doi.org/10.1093/cercor/bhac072
Advance access publication date 24 March 2022
Original Article

Aberrant motor contagion of emotions in psychopathy and high-functioning autism

Lihua Sun[1,2,3,*], Lasse Lukkarinen[1,2,4,5,†], Tuomo Noppari[6,†], Sanaz Nazari-Farsani[1], Vesa Putkinen[1], Kerttu Seppälä[1,7], Matthew Hudson[1], Pekka Tani[6], Nina Lindberg[8], Henry K. Karlsson[1], Jussi Hirvonen[9], Marja Salomaa[4], Niina Venetjoki[4], Hannu Lauerma[4,5,10], Jari Tiihonen[11,12,13], Lauri Nummenmaa[1,2,14]

[1]Turku PET Centre, University of Turku, Turku FI-20521, Finland,
[2]Turku PET Centre, Turku University Hospital, Turku FI-20521, Finland,
[3]Department of Nuclear Medicine, Huashan Hospital, Fudan University, Shanghai, 200040, China,
[4]Psychiatric Hospital for Prisoners, Health Care Services for Prisoners, Turku FI-20251, Finland,
[5]Department of Psychiatry, Turku University Hospital, Turku FI-20251, Finland,
[6]Department of Psychiatry, Helsinki University Hospital, Helsinki FI-00014, Finland,
[7]Department of Medical Physics, Turku University Hospital, Turku, Finland,
[8]Department of Forensic Psychiatry, Helsinki University Hospital, University of Helsinki, Helsinki FI-00014, Finland,
[9]Department of Radiology, University of Turku and Turku University Hospital, Turku FI-20251, Finland,
[10]Department of Psychiatry, University of Turku, Turku FI-20251, Finland,
[11]Department of Clinical Neuroscience, Karolinska Institute, Stockholm SE-11364, Sweden,
[12]Center for Psychiatry Research, Stockholm City Council, Stockholm SE-11364, Sweden,
[13]Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio FI-70240, Finland,
[14]Department of Psychology, University of Turku, Turku FI-20251, Finland
*Corresponding author: Turku PET Centre, University of Turku, Kiinamyllynkatu 4-8, Turku FI-20521, Finland. Email: lihua.sun@utu.fi

[†]Equal contribution (Lasse Lukkarinen and Tuomo Noppari)

Psychopathy and autism are both associated with aberrant social skills and empathy, yet only psychopaths are markedly antisocial and violent. Here, we compared the functional neural alterations underlying these two groups that both have aberrant empathetic abilities but distinct behavioral phenotypes. We studied 19 incarcerated male offenders with high psychopathic traits, 20 males with high-functioning autism, and 19 age-matched healthy controls. All groups underwent functional magnetic resonance imaging while they viewed dynamic happy, angry, and disgusted faces or listened to laughter and crying sounds. Psychopathy was associated with reduced somatomotor responses to almost all expressions, while participants with autism demonstrated less marked and emotion-specific alterations in the somatomotor area. These data suggest that psychopathy and autism involve both common and distinct functional alterations in the brain networks involved in the socioemotional processing. The alterations are more profound in psychopathy, possibly reflecting the more severely disturbed socioemotional brain networks in this population.

Key words: psychopathy; autism; emotion; sociality; motor cortex.

Introduction

The ability to relate with others is a fundamental human skill that is highly automated. Effortless flow of emotional states and goals across individuals facilitates the understanding of intentions and actions and allows us to "tune in" with others (Hatfield et al. 1993; Keysers et al. 2010; Nummenmaa et al. 2012). However, there exists marked variation in the ability to understand others' needs and goals as well as to take these into account in social interactions. Psychopathy is an extreme case of lacking ability to relate with others despite of the skillful manipulativeness to achieve goals among social interactions (Wilson 1994). It is characterized by recurring antisocial behavior, bold, disinhibited, and egotistical traits, and lacking empathy and remorse (Cooke and Michie 2001). Psychopathy is also causally linked with criminal behavior and violence (Murrie et al. 2004). While the prevalence of psychopathy is around 1% in normal population, it is around 20% in incarcerated offenders (Hare 2003) and 16.4% in Finnish incarcerated offenders (Jüriloo et al. 2014). Because these behavioral and emotional symptoms are persistent and present already in childhood, psychopathy likely has an organic basis.

Neuroimaging studies have found that psychopathic offenders have lower volume in the frontal cortex and in limbic regions, including insula and amygdala (Müller et al. 2008; Tiihonen et al. 2008; Yang et al. 2009; Ermer et al. 2012; Nummenmaa et al. 2021). These structural

Received: November 16, 2021. **Revised:** February 1, 2022. **Accepted:** February 8, 2022
© The Author(s) 2022. Published by Oxford University Press.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

alterations are accompanied with abnormal responsiveness of the limbic system. Psychopathy is associated with weaker activity in the amygdala and hippocampus, striatum, and cingulate cortices while viewing emotional facial expressions. Psychophysiological and neuroimaging studies have revealed that participants with psychopathic traits show significantly reduced autonomic nervous system responses and frontocortical brain activity toward others' distress, which is consistent with lowered care motivation (Decety et al. 2013; Meffert et al. 2013). Conversely, stronger responses are observed in the frontal cortical regions (Kiehl et al. 2001; Dolan and Fullam 2009), particularly when viewing violent emotional episodes (Nummenmaa et al. 2021). The distorted limbic outputs combined with dysfunction in executive frontal cortical and social decision-making systems could thus predispose psychopaths to violent and antisocial behavior (Contreras-rodríguez et al. 2014; Contreras-Rodríguez et al. 2015).

Difficulty in relating with other people is a common feature of the autistic and psychopathic phenotype (Marsh 2018). Autism spectrum disorders (ASDs) are also characterized by abnormalities and difficulties in the social domain, and similarly as psychopathy, they have an early onset and neurodevelopmental origin. ASDs are typically manifested as aberrant communication, restricted interests, repetitive behavior, and sensory anomalies (Battle 2013; Lord et al. 2020). ASDs have variable clinical phenotypes from mild to severe, and even wider continuum of social-communicative ability extending into the general population has been proposed (Vecera and Marron 1996; Baron-Cohen et al. 2001). Neuroimaging studies have linked ASD with aberrant structure and function in socioemotional brain networks, such as those involved in the processing of goal-directed actions and biological motion (superior temporal sulcus), theory of mind (medial prefrontal cortex and temporoparietal junction), and emotion (amygdala) (Harms et al. 2010; Uljarevic and Hamilton 2013; Glerean et al. 2016). Similar to psychopathy, ASD is associated with reduced limbic activation by emotional stimuli, such as happy, fearful, and disgusted faces (Ogai et al. 2003; Kim et al. 2015). It is however controversial whether aberrant socioemotional processing pertains to all emotions versus only a subset of them, and even meta-analyses have provided evidence for both general (Lozier et al. 2014) and emotion-specific effects (Uljarevic and Hamilton 2013).

ASD and psychopathy have a set of common and distinct characteristics. Both ASD and psychopathy are both overrepresented in forensic settings (Im 2016), and aggression is also somewhat common in autistic samples (Kanne and Mazurek 2011). Because early onset childhood conduct disorder is highly predictive of adult psychopathy, it can also be seen as a neurodevelopmental disorder similarly as ASD (Raine 2018). Both ASD and psychopathy are also heritable and may have shared genetic basis (O'Nions et al. 2015; Tiihonen et al. 2020). Despite these shared features, the behavioral phenotypes in psychopathy and ASD also differ in important ways. First, although ASD might be underdiagnosed in forensic settings (Loureiro et al. 2018), the available data show that antisocial behavior is more common in psychopathy than in ASD. Second, while psychopathic individuals can use their superficial charm and glib for manipulating other people (Wilson 1994), autistic individuals have, in general, severe difficulties in maintaining even routine social interactions. Third, the nonsocial domains of ASD (restricted interests, repetitive behavior, and sensory anomalies) are not manifested in psychopathy, which is better characterized by impulsive rather than highly structured behavioral patterns (Cooke and Michie 2001); intellectual disabilities are also not common in psychopaths who tend to be of average intelligence (Hare 2003). Finally, while psychopathy is characterized by impaired mental state attribution for others' emotions, ASD is associated with impaired cognitive perspective-taking (Jones et al. 2010; Marsh and Cardinale 2012; Lockwood et al. 2013).

Taken together, individuals with both autism and psychopathy can act in ways that implicate lack of empathy toward others, and aberrant functioning in comparable brain systems have been implicated in both conditions. Comparison between autistic and psychopathic individuals' neural response to socioemotional signals would thus provide a unique opportunity for addressing whether specific perturbations of the socioemotional brain networks are linked with distinct social and antisocial behavioral patterns. However, to our knowledge, no prior study has directly compared functional brain basis of psychopathy and autism.

The current study

In the current study, we compared neural responses to emotional communicative signals in healthy controls versus incarcerated psychopathic offenders and individuals with ASD. All groups underwent functional magnetic resonance imaging (fMRI) while they viewed dynamic happy, angry, and disgusted facial expressions or listened to laughter and crying sounds. We show that psychopathy is associated with reduced somatomotor responses to almost all expressions, while in ASD, comparable alterations were found only for laughter and disgusted facial expressions. Direct comparison revealed that downregulation of the somatomotor responses to all facial expressions was larger in psychopathy versus ASD.

Methods

Subjects

We studied 19 convicted male offenders with high psychopathic traits, 20 males with high-functioning autism, and 19 age-matched healthy controls. Exclusion criteria were psychotic or other severe psychiatric illnesses, autoimmune illnesses, use of opioids, antipsychotic medication other than very small doses for insomnia, current substance abuse, exceptional risk of violence, claustrophobia, and other contraindications for magnetic

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

resonance imaging. The study was approved by the ethical committee of the Hospital District of Southwest Finland and was conducted in accordance of the Helsinki declaration. All participants completed informed consent forms prior to participating.

Convicted offenders

Offenders were inmates of the Turku Prison and they had been sentenced for murder ($n = 5$), manslaughter ($n = 5$), attempted manslaughter ($n = 3$), or grievous bodily harm ($n = 6$). Information regarding the study was distributed to the inmates potentially eligible for the study, and volunteers were then evaluated by the prison hospital psychiatrists. Psychiatric diagnoses for offenders were based on prison health care and forensic psychiatric violence risk assessments, forensic psychiatric examination reports concerning legal responsibility, 2 recruitment interviews, and semistructured Psychopathy Checklist-revised (PCL-R) interviews. Final consensus diagnoses were made by two medical specialists (M.S. and H.L.), both with 13–25 years of experience in the field of prison psychiatry, which was also assisted by a psychologist (N.V.) with a 15-year working history in the Psychiatric Hospital for Prisoners. Offenders were escorted by 2 prison guards to the local research institute for the brain imaging study. More detailed clinical information of offenders is found in Supplementary Table S1.

None of the offender group was psychotic nor suffered from a significant mood disorder, as assessed via a SCID-I interview (Spitzer et al. 1992). The group consisted of 16 participants with antisocial personality disorders, as defined by DSM-5 criteria (Battle 2013), and 3 who did not fulfill the criterion of conduct disorder before the age of 15 years but only the other criteria of antisocial personality. History of excessive alcohol use was present in 13 participants, and 18 participants had self-reported or documented use of illegal substances, including black market benzodiazepines, pregabalin or opioids, cannabis, amphetamines, gamma-hydroxybutyrate, MDPV, anabolic steroids, and cocaine. Information concerning the severity of abuse was considered unreliable.

Psychopathy scores of the offenders were evaluated with semistructured interview by experienced forensic psychiatrists or psychologists based on the PCL-R (Hare 2003); Levenson Self-Report Psychopathy Scale (LSRP) questionnaires (Levenson et al. 1995) for offenders were also documented as untrusted data. Psychopathy scores of healthy controls and participants with ASD were based on the LSRP questionnaire. LSRP measures 2 dimensions of psychopathy, with the primary psychopathy score indicating inclination to lie, lack of remorse, and callousness and the secondary psychopathy score indicating impulsivity, short temper, and low toleration for frustration.

Participants with ASD

Participants in the ASD group were volunteers from the Helsinki and Turku University Hospital Neuropsychiatric Clinic, and 1 participant was also recruited from the Neuropsychiatric Clinic Proneuron in Espoo. Based on patient history, accessible information from births records, well-baby clinics, and school health care, the ASD diagnoses were verified by research psychologist, neurologist, and psychiatrist following the DSM-5 criteria. An additional current Autism Diagnostic Observation Schedule (ADOS) assessment (Lord et al. 2012) was also used to clarify the ASD diagnostics. All ASD participants were diagnosed with ASD, 6 also with ADHD and 8 with other mood and anxiety disorders. Healthy participants and ASD group also completed the autism-spectrum quotient (AQ) questionnaire (Bishop et al. 2004). None of the ASD participants had currently severe mental disorder, as assessed via the SCID-I interview. Dopaminergic medications (antipsychotics, psychostimulants, and bupropion) were withdrawn before measurements, but 4 participants who had SSRI medication could not be withdrawn. Clinical information of the ASD participants is found in Supplementary Table S2.

Healthy controls

The control participants were screened for medical conditions from their patient histories, and their use of prescribed medication was double-checked from the Finnish medical database. Clinical information of the control participants is found in Supplementary Table S3.

Facial expression task

In the emotional facial expression task (Fig. 1A), participants viewed short video clips (5 s) of dynamic facial expressions of joy, disgust, and anger selected from ADFES database (van der Schalk et al. 2011). All clips begun with a neutral face, which was followed by a dynamic display of the facial expression. Prior to each clip, participants were shown the first frame of the video (i.e. neutral face) for 3.5 s to avoid peaks in low-level visual activation due to simultaneous visual stimulus and motion onset. This was followed by the dynamic expression from neutral to full expression, with the full-blown phase held until the end of the clip. Each stimulus was followed by a random 4–8 s of rest period. Again, to avoid peaks in low-level visual cortical activations, a scrambled picture of the upcoming model was shown during the rest period. To keep participants focused on the task, 4 trials (out of 36 trials in total) contained a still picture of the neutral face instead of the video clip. Participants were asked to press the response button as soon as they detected a trial without any facial motion. These trials were excluded from the analysis. Previous work shows that these dynamic stimuli elicit consistent and expression-specific neural responses in emotion and face perception circuits (Volynets et al. 2020).

Vocal expression task

In the vocal expression task (Fig. 1B), the participants listened to short laughter and crying vocalizations and control stimuli which were generated by time-domain

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

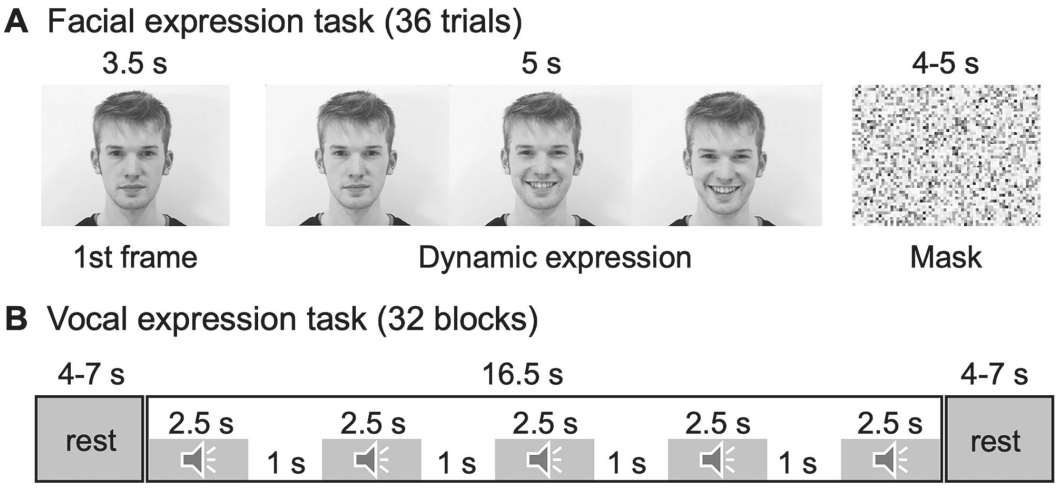


Fig. 1. Experimental design for the facial expression task A) and vocal expression task B). Color images and videos were used in the facial expression task.

scrambling of the original sounds. The original stimuli have been validated and described in detail in O'Nions et al. (2017). The experiment was run using a blocked design. In each 16.5-s block, 5 2.5-s stimuli from 1 category (i.e. laughter, crying sounds, scrambled laughter, or scrambled crying sounds) were played with a 1-s silent period between stimuli. Order of the blocks were randomized. The blocks were interspersed with rest blocks lasting for 4–7 s. To keep participants focused on the task, an animal sound (vocalization of an alpaca) was presented randomly during 50% of the rest blocks. The participants were instructed to press the response button whenever they heard the alpaca, and the behavioral outcomes were inspected for the focus of attention. A total of 32 blocks (8 blocks per stimulus type) were run.

fMRI acquisition and preprocessing

The magnetic resonance imaging (MRI) data were acquired with Phillips Ingenuity TF PET/MR 3T whole-body scanner. High-resolution (1 mm^3) structural brain images were acquired using a T1-weighted (T1w) sequence (time repetition [TR] = 9.8 ms, time echo [TE] = 4.6 ms, flip angle = 7°, 250 mm FOV, 256 × 256 reconstruction matrix). Radiologist screened the images for structural abnormalities. Functional data were acquired using a T2∗-weighted echo-planar imaging sequence (TR = 2600 ms, TE = 30 ms, 75° flip angle, 240 mm FOV, 80 × 80 reconstruction matrix, 62.5 kHz bandwidth, 3.0 mm slice thickness, 45 interleaved slices acquired in ascending order without gaps). A total of 206 (facial expression task) or 290 (laughter task) functional volumes were acquired. We used fMRIPrep 1.3.0.2 to preprocess the MRI data (Esteban et al. 2019). Anatomical T1w reference images were processed following steps: correction for intensity nonuniformity, skull-stripping, brain surface reconstruction, spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov et al. 2009) using nonlinear registration with antsRegistration (ANTs 2.2.0), and brain tissue segmentation. fMRI data were processed following steps: coregistration to the T1 reference image, slice-time correction, spatial smoothing with a 6-mm Gaussian kernel, automatic removal of motion artifacts using ICA-AROMA (Pruim et al. 2015), and resampling to the MNI152NLin2009cAsym standard space. Quality of images was assessed via the visual reports of fMRIPrep and was inspected manually in accord to the whole-brain field of view coverage, proper alignment to the anatomical images, and signal artifacts. All functional data were retained in the analysis. Quality of images was visually checked and also inspected based on fmriprep's visual reports. No images had >25% of frames with >1-mm frame displacement (Parkes et al. 2018).

Full-volume GLM data analysis

The fMRI data were analyzed in SPM12 (Wellcome Trust Center for Imaging, London, UK, (http://www.fil.ion.ucl.ac.uk/spm). The whole-brain random effects model was applied using a 2-stage process with separate first and second levels. For each participant, GLM was used to predict the regional effects of task parameters on blood oxygen level–dependent (BOLD) indices of activation. In the facial expression task, contrast images were generated for dynamic happy, angry, or disgusted facial expressions versus static neutral faces (i.e. the initial 3.5 s of each video without motion) and were subjected to second-level analyses for population-level inference. In the vocal expression task, contrast images were generated for laughter or crying sound versus corresponding scrambled sounds and were subjected to second-level analyses. We first tested the task-dependent activations in each group and conducted the between-group comparisons for each effect of interest. In addition to between-group comparisons, in a control analysis, we also fitted a multi-

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

Table 1. Basic characteristics of the participants.

Groups	Control	ASD	Psychopathy
Age	28.53 (7.69)	27.85 (5.56)	31.16 (6.49)
Education level			
Interrupted primary school	0	0	2
Primary school	0	3	12
Second degree	10	14	5
University degree	9	3	0
Psychopathy			
PCL-R	—	—	26.47 (6.24)
LSRP primary psychopathy	21.95 (3.05)	23.30 (3.95)	30.67 (5.96)[a]
LSRP secondary psychopathy	13.47 (2.97)	16.60 (3.28)	19.8 (3.14)[a]
Autism			
AQ	10.95 (3.44)	27.65 (5.64)	19.63 (6.43)[a]
ADOS	—	11.30 (4.34)	—

Note: — indicates data not available. [a]Indicates data not trusted.

ple regression model where the primary LSRP scores and AQ scores were used as regressors. By controlling the effect of the other, this provided additional information regarding the specific effect of these factors across all the subject groups. The secondary LSRP scores were significantly correlated with the AQ scores when the groups were pooled ($r = 0.37$, $P = 0.005$) and therefore were not applied in the control analysis. Statistical threshold was set at $P < 0.05$, FDR-corrected at cluster level.

Region of interest analysis

To visualize the between-group differences, BOLD signals in anatomically defined regions of interest (ROIs) were also analyzed. ROIs were selected considering their important roles in socioemotional processing. These ROIs included anterior, middle, and posterior cingulate cortices (CCs), precuneus, amygdala, caudate, putamen, and insula defined by the AAL atlas (Tzourio-Mazoyer et al. 2002). We also included the subregions of motor area, which are parceled in the Juelich Atlas with masks generated using the SPM Anatomy toolbox (Eickhoff et al. 2005). These subregions include the primary motor cortex (M1) corresponding to Brodmann areas (BAs) 4a and 4b; the supplementary motor area (M2) corresponding to BA6 (Geyer 2004); the primary somatosensory cortex (S1), including BA3a, BA3b, BA1, and BA2 (Geyer et al. 2000; Grefkes et al. 2001); and the secondary somatosensory cortex (S2), including parietal operculum 1-4 (Eickhoff et al. 2006). Regional beta weights were estimated from first-level contrast images of each participant using the MarsBaR toolbox (Brett et al. 2002). ROI data were analyzed using 2-sample t-test in R statistical software (version 3.6.3).

Results

Psychopathy and autism evaluation in the studied groups

Basic information of participants is summarized in Table 1.

In the psychopathy group, interview based PCL-R measures were conducted since their self-reported data were considered unreliable due to the nature of psychopathy. This was also supported by a lack of significant correlation for PCL-R scores with either primary LSRP scores ($r = 0.3$, $P = 0.3$) or secondary LSRP scores ($r = 0.23$, $P = 0.4$). However, both primary and secondary LSRP scores of the psychopathy group were significantly higher than the other groups (Supplementary Fig. S1).

In the ASD group, AQ scores were significantly higher compared to controls ($t = 11.14$; $P < 0.001$). While there was no statistical difference between ASD group and controls for LSRP primary psychopathy scores ($t = 1.20$; $P = 0.24$), the ASD group had higher secondary psychopathy score ($t = 3.12$; $P = 0.003$).

Regional responses to positive emotional stimuli

In the control group, happy faces elicited activation in the occipital cortex; fusiform gyrus; CC; motor area, including the primary (S1) and secondary (S2) somatosensory cortex and primary (M1) and supplementary motor (M2) areas; medial frontal cortex (MFC); middle temporal gyrus (MTG) and superior temporal gyrus (STG); precuneus; cuneus; amygdala; hippocampus; striatum; and thalamus (Fig. 2A). Social laughter sounds elicited activation in the primary and secondary auditory cortices, CC, motor area, MFC, MTG, and STG, precuneus, amygdala, hippocampus, striatum, and thalamus. These activations by both happy faces and laughter were weakened in the autistic individuals and were markedly abolished in the psychopathy group, with the exception of the temporal activations (Fig. 2A). In the psychopathy group, large-scale deactivation was also observed for laughter.

This was confirmed in direct between-group contrasts (Fig. 2B). Compared to controls, the psychopathy group showed dampened responses to happy faces and laughter in motor area, CC, and precuneus. Dampened activation in response to laughter expanded largely to frontal and posterior brain areas and subcortical regions. Compared to controls, ASD group showed dampened responses in the middle and anterior CCs to happy faces and in the motor area (also expanding frontally) to laughter. Compared to ASD group, psychopathy group showed dampened response in motor area to happy faces and in precuneus to laughter.

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

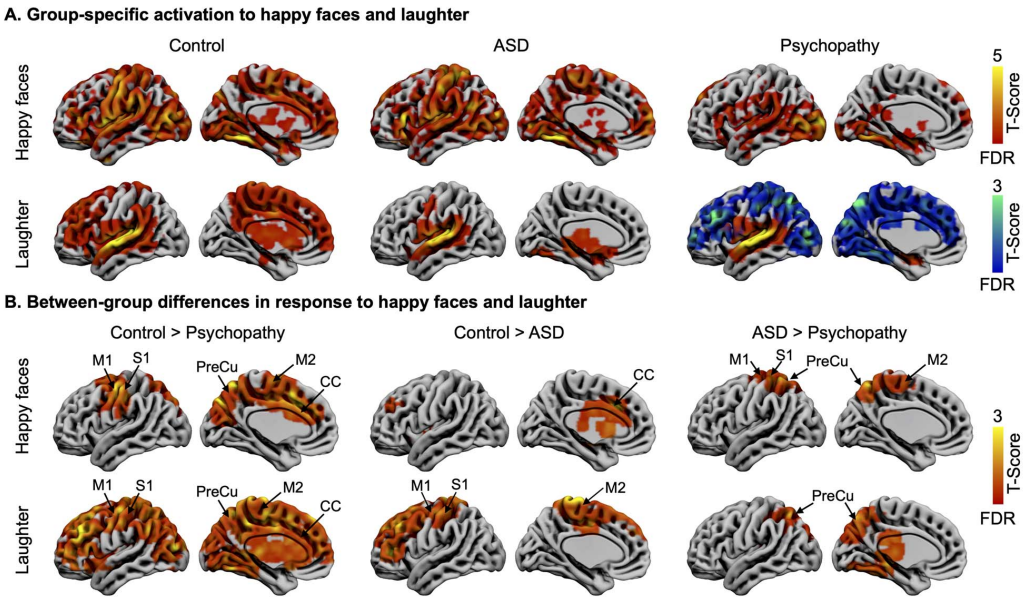


Fig. 2. Brain responses to happy faces and social laughter. A) Responses to happy faces and laughter separately for each group. Hot color indicates activation and cool color indicates deactivation. B) Between-group differences in response to happy faces and laughter. Data are thresholded at $P < 0.05$ with FDR cluster-level correction. S1 = primary somatosensory cortex, S2 = secondary somatosensory cortex, M1 = primary motor cortex, M2 = supplementary motor area, and PreCu = precuneus.

Regional responses to negative emotional stimuli

In controls, both angry and disgusted faces elicited activation in the occipital cortex, FFA, CC, the motor area, MFC, MTG and STG, precuneus, amygdala, hippocampus, striatum, and thalamus (Fig. 3A). Comparable activation of these regions was found in autistic individuals, while similarly as for happy faces and laughter, activities in these brain regions in psychopathic individuals were markedly abolished (Fig. 3A).

This was also confirmed in direct between-group contrast (Fig. 3B). Compared to controls, participants with psychopathy showed dampened activation in CC, motor area, and precuneus to both angry and disgusted faces. Compared to controls, ASD group also showed dampened activation in the CC, motor area, and precuneus to disgusted faces. However, in response to angry faces, ASD group showed increased activation in precuneus and posterior CCs. Compared to ASD group, the psychopathy group showed global deactivation to angry faces and damped activation in motor area and precuneus to disgusted faces.

Crying sound elicited activation mainly in the primary and secondary auditory cortices and in nearby regions (Supplementary Fig. S2). However, group comparisons did not show statistical differences. We also investigated whether the self-reported LSRP and AQ scores, while controlling for each other, were specifically associated with brain responses to the facial and vocal expression stimuli (Supplementary Fig. S3). In line with the group-level findings, data showed that LSRP primary score was specifically associated with reduced response to laughter in the CC, thalamus lateral prefrontal cortex, somatomotor area, and precuneus. Also, AQ score was specifically associated with increased brain response to angry faces in CC, somatomotor area, and precuneus.

ROI analysis

ROI analysis demonstrated between-group differences that were in accord with the full-volume analysis (Fig. 4). In response to laughter (Fig. 4A), psychopathy group showed reduced activation in M1, M2, S1, and the combined somatomotor areas (M1, M2, S1, and S2 together), anterior cingulate cortex (ACC), and middle cingulate cortex (MCC) compared to controls. There were no statistically significant differences between controls and ASD group, although numerically mean activity was strongest in controls and weakest in psychopathy group in most ROIs.

In response to angry faces (Fig. 4B), psychopathy group demonstrated reduced activation in ROIs, including the M1, S2, whole motor area, ACC, MCC, and posterior cingulate cortex (PCC) compared to ASD group. ASD group also showed increased activation in the PCC compared to controls. No between-group differences were found for crying sounds and happy faces. For disgusted faces, psychopathy group showed reduced activation in MCC compared to controls (data not shown). Subcortical BOLD

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

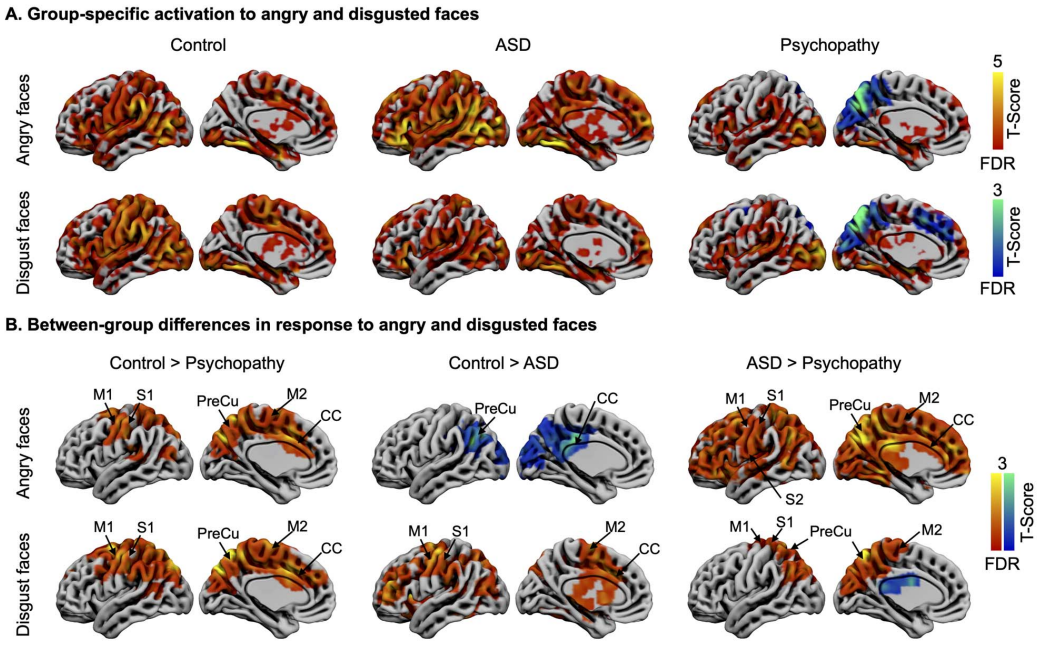


Fig. 3. Brain responses to angry and disgusted faces. A) Responses to angry and disgusted faces separately for each group. B) Between-group differences in responses to angry and disgusted faces. Data are thresholded at $P < 0.05$ with FDR cluster-level correction.

activity in the amygdala, insula, and striatum did not show between-group differences in the tasks.

Discussion

Incarcerated offenders with psychopathic traits and patients with high-functioning autism showed both common and unique alterations in the brain responses to positive and negative facial and vocal social communicative signals. Compared with controls, offenders showed lowered brain activation toward all communicative signals except for crying sounds. Weaker activity was observed in somatosensory, motor, and CC. This effect was less pronounced in the patients with ASD and was observed primarily for laughter and disgusted facial expressions. Direct comparison between psychopathic offenders and patients with ASD revealed that the somatomotor responses were weaker in offenders. Altogether, our data show that alterations in somatomotor processing of emotional signals is a common characteristic of criminal psychopathy and autism, yet the degree and specificity of these alterations distinguishes between these two groups. The higher overall degree of alterations in the psychopathic offenders might explain this phenotype manifested by both lacking the ability to relate with others as well as violent behavior.

Our main finding was that somatomotor "mirroring" of vocal and facial emotional expressions was altered in both criminal offenders and participants with ASD and that the somatosensory and motor responses to emotional signals were more reduced in the criminal offenders than in the ASD group. This accords with previous studies that have found reduced brain activation during passive observation of others' distress (Meffert et al. 2013) or affective memory tasks (Kiehl et al. 2001) in participants with psychopathic traits. Psychopathic offenders also show less behavioral contagion of laughing and yawning (Hagenmuller et al. 2012), and recent structural imaging study demonstrated that both criminal psychopathy as well as psychopathy-like traits in healthy controls are associated with lower volume in the somatosensory cortices (Nummenmaa et al. 2021).

Seeing others in a particular emotional state often triggers automatically the corresponding behavioral and somatic representation of that emotional state in the observer (Dimberg and Thunberg 1998; Wild et al. 2001). Neuroimaging studies have confirmed that such somatomotor contagion of emotions is subserved by common neural activation for the perception and experience of states, such as pain (Singer et al. 2004; Jackson et al. 2005; Saarela et al. 2007), disgust (Wicker et al. 2003), and pleasure (Jabbi et al. 2007), allowing to "tune in" or "sync" with other individuals (Keysers et al. 2010; Nummenmaa et al. 2012). Furthermore, damage to somatosensory cortex (Adolphs et al. 2000) and their inactivation by transcranial magnetic stimulation (Pourtois et al. 2004) also

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

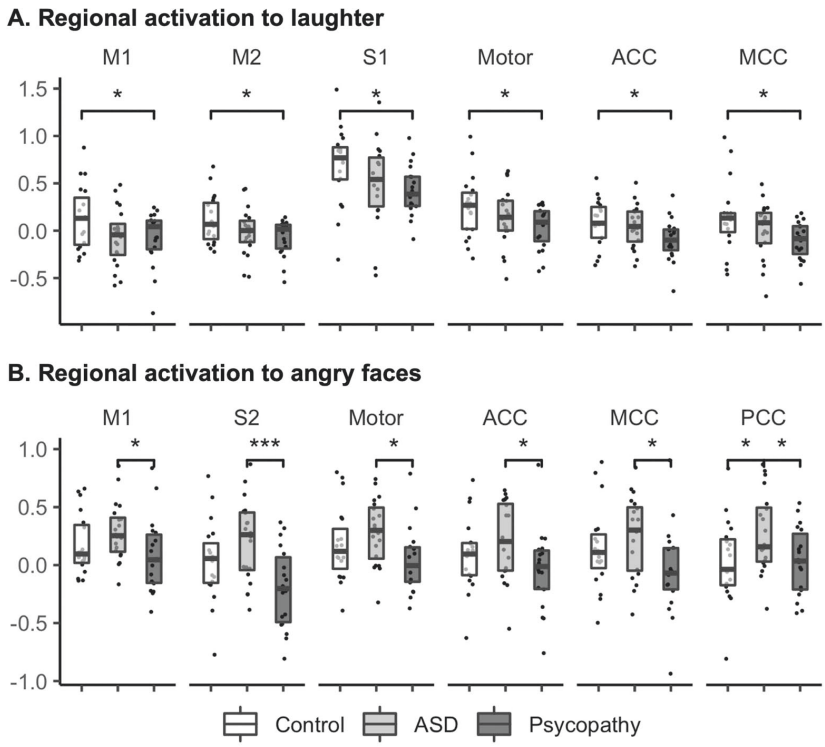


Fig. 4. Region-of interest analysis for laughter (A) and angry faces (B). Between group comparisons were conducted using student's *t*-test, with significance levels marked: *$P < 0.05$, ***$P < 0.01$. motor = combined region of M1, M2, S1, and S2; data involved both hemispheres.

impair recognition of emotions from facial expressions. The widespread aberrant responsivity of the somatosensory cortex in psychopathic offenders may explicate their asocial character, lack of empathy, and egotistical traits (Cooke and Michie 2001). As mirroring of others' emotions and particularly distress plays a crucial role in empathy and inhibition of violent behavior (Blair 2001; Karjalainen et al. 2017), impaired somatic and motor contagion of others' emotions may render psychopaths susceptible to antisocial behavior and violence.

The participants with ASD also had lowered somatomotor responses to emotional signals, although this effect was less profound than in the offenders. Prior work shows that autistic individuals have difficulties in recognizing specific emotions (Clark et al. 2008; Harms et al. 2010; Uljarevic and Hamilton 2013) as well as difficulties in automatic mimicking facial expressions (McIntosh et al. 2006; Oberman et al. 2009). Some studies have also shown that patients with ASD have deficient motor intention understanding ability, which is possibly linked with aberrant motor cognition (Cattaneo et al. 2007; Boria et al. 2009; Casartelli et al. 2016). In line with these studies, functional neuroimaging experiments show that high-functioning autism hinders the brain from synchronizing with those of others while viewing naturalistic social interaction, which is indicative of aberrant automatic tuning in with others' mental states (Hasson et al. 2009; Salmi et al. 2013). The present data highlight how the aberrant activity of the somatosensory and motor cortices may also contribute to these impairments.

Although both psychopathy and ASD groups showed, in general, reduced responses to the vocal and facial emotional expressions, the specific patterns of these alterations differed across the groups. Overall, the emotional expressions evoked weaker responses in the psychopathic than autistic individuals, and for all facial expressions, this effect was observed in the primary somatosensory, primary, and supplementary motor cortices. Because motor responses to social communicative signals are fundamental for establishing social bonds between individuals (Iacoboni et al. 2005; Keysers and Gazzola 2007) and are important for the formation of empathic responses (Gallese 2001; Leslie et al. 2004; Warren et al. 2006), the present observed aberrant motor contagion may reflect the shared component of the socioemotional deficits in autism and psychopathy. Laughter expressions elicited to large-scale deactivation outside the auditory cortices only in offenders. Laugher is a universally recognized prosocial signal that is used for bonding purposes, rather than an expression of positive emotional state (Scott et al. 2014),

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

and many of the characteristics defining psychopathy are related to abnormal socioemotional interaction. It is thus possible that the aberrant neural responses to bonding signals, such as laughter, could link with the antisocial traits in psychopathy. Additionally, for angry faces, the difference between psychopathy and ASD groups was markedly widespread, with psychopathy group showing significantly reduced responses across the medial and lateral frontal cortices in comparison with the autistic patients. These data suggest that autism-associated hypersensitivity of the neural systems responding to anger and hyposensitivity to prosocial cues, such as laugher, may explain the distinct patterns of social interaction and communication deficits in psychopathy and autism.

The current study also bears limitations. Although we aimed at recruiting prisoner volunteers not using antipsychotics, antidepressants, or anxiolytics, it was not possible to recruit a completely drug-naive sample. The convicted offenders and healthy controls and participants with ASD also differ from each other regarding the available quality and quantity of social interaction, leisure time activities, education levels, and so forth. Ideally, this kind of study should thus also involve a forensic but nonpsychopathic sample. Despite of these mentioned limitations, however, our reported between-group differences were supported by the control analysis based on cautiously trusted common measures. Our data are cross-sectional in nature and cannot resolve the potential causal link between the functional alterations and psychopathy and autism. Further, because our focus was on criminal psychopathy, we decided against completing the laborious and time-consuming PCL-R protocol for the healthy and nonincarcerated sample. We only included male participants in the current study and findings may not generalize to females.

In summary, our findings suggest that aberrant neural activity in somatomotor areas may be a common mechanism underlying the asocial behavior in psychopathy and autism, while its severity and selectivity in response to different types of social communicative signals set these disorders apart. These data suggest that distinct conditions associated with social information processing abnormalities might share common neurobiological substrates despite distinct behavioral and clinical phenotypes.

Acknowledgments

We thank director Juhani Järvi and other staff members of Turku Prison who made it possible to safely guard and transport the inmates during the neuroimaging.

Supplementary material

Supplementary material is available at *Cerebral Cortex Journal* online.

Funding

The study was supported by the Academy of Finland (grants no. 294897 and 332225), and Valon Vuoksi Foundation (grants to L.S. and L.L.). L.S. is personally supported by the Turku Collegium for Science and Medicine, University of Turku.

Conflict of interest statement. None declared.

References

Adolphs R, Damasio H, Tranel D, Cooper G, Damasio AR. A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *J Neurosci*. 2000:20:2683–2690.

Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord*. 2001:31:5–17.

Battle DE. Diagnostic and statistical manual of mental disorders (DSM). *CoDAS*. 2013:25:191–192.

Bishop DVM, Maybery M, Maley A, Wong D, Hill W, Hallmayer J. Using self-report to identify the broad phenotype in parents of children with autistic spectrum disorders: a study using the autism-spectrum quotient. *J Child Psychol Psychiatry Allied Discip*. 2004:45:1431–1436.

Blair RJR. Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. *J Neurol Neurosurg Psychiatry*. 2001:71:727–731.

Boria S, Fabbri-Destro M, Cattaneo L, Sparaci L, Sinigaglia C, Santelli E, Cossu G, Rizzolatti G. Intention understanding in autism. *PLoS One*. 2009:4.

Brett M, Anton J-LL, Valabregue R, Poline J-B. Region of interest analysis using an SPM toolbox. *NeuroImage*. 2002:16:497.

Casartelli L, Molteni M, Ronconi L. So close yet so far: motor anomalies impacting on social functioning in autism spectrum disorder. *Neurosci Biobehav Rev*. 2016:63:98–105.

Cattaneo L, Fabbri-Destro M, Boria S, Pieraccini C, Monti A, Cossu G, Rizzolatti G. Impairment of actions chains in autism and its possible role in intention understanding. *Proc Natl Acad Sci U S A*. 2007:104:17825–17830.

Clark TF, Winkielman P, McIntosh DN. Autism and the extraction of emotion from briefly presented facial expressions: stumbling at the first step of empathy. *Emotion*. 2008:8:803–809.

Contreras-rodríguez O, Pujol J, Batalla I, Harrison BJ, Bosque J, Ibernregàs I, Hernández-ribas R, Soriano-mas C, Deus J, López-solà M, et al. Disrupted neural processing of emotional faces in psychopathy. *Soc Cogn Affect Neurosci*. 2014:9:505–512.

Contreras-Rodríguez O, Pujol J, Batalla I, Harrison BJ, Soriano-Mas C, Deus J, López-Solà M, Macià D, Pera V, Hernández-Ribas R, et al. Functional connectivity bias in the prefrontal cortex of psychopaths. *Biol Psychiatry*. 2015:78:647–655.

Cooke DJ, Michie C. Refining the construct of psychopathy: towards a hierarchical model. *Psychol Assess*. 2001:13:171–188.

Decety J, Skelly LR, Kiehl KA. Brain response to empathy-eliciting scenarios involving pain in incarcerated individuals with psychopathy. *JAMA Psychiat*. 2013:70:638–645.

Dimberg U, Thunberg M. Rapid facial reactions to emotional facial expressions. *Scand J Psychol*. 1998:39:39–45.

Dolan MC, Fullam RS. Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

to emotional faces in violent patients with schizophrenia. *Biol Psychiatry*. 2009:66:570–577.
Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*. 2005:25:1325–1335.
Eickhoff SB, Schleicher A, Zilles K, Amunts K. The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. *Cereb Cortex*. 2006:16:254–267.
Ermer E, Cope LM, Nyalakanti PK, Calhoun VD, Kiehl KA. Aberrant paralimbic gray matter in criminal psychopathy. *J Abnorm Psychol*. 2012:121:649–658.
Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, Kent JD, Goncalves M, DuPre E, Snyder M, et al. fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nat Methods*. 2019:16:111–116.
Fonov V, Evans A, McKinstry R, Almli C, Collins D. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage*. 2009:47:S102.
Gallese V. The "shared manifold" hypothesis: from mirror neurons to empathy. *J Conscious Stud*. 2001:8:33–50.
Geyer S. The microstructural border between the motor and the cognitive domain in the human cerebral cortex. *Adv Anat Embryol Cell Biol*. 2004:174:1–89.
Geyer S, Schormann T, Mohlberg H, Zilles K. Areas 3a, 3b, and 1 of human primary somatosensory cortex. 2. Spatial normalization to standard anatomical space. *NeuroImage*. 2000:11:684–696.
Glerean E, Pan RK, Salmi J, Kujala R, Lahnakoski JM, Roine U, Nummenmaa L, Leppämäki S, Nieminen-von Wendt T, Tani P, Saramäki J, Sams M, Jääskeläinen IP. Reorganization of functionally connected brain subnetworks in high-functioning autism. *Hum Brain Mapp*. 2016:37:1066–1079.
Grefkes C, Geyer S, Schormann T, Roland P, Zilles K. Human somatosensory area 2: observer-independent cytoarchitectonic mapping, interindividual variability, and population map. *NeuroImage*. 2001:14:617–631.
Hagenmuller F, Rössler W, Endrass J, Rossegger A, Haker H. Empathische Resonanzfähigkeit bei Straftätern mit psychopathischen Persönlichkeitszügen. *Neuropsychiatrie*. 2012:26:65–71.
Hare RD. *The Hare psychopathy checklist— revised*. 2nd ed. Toronto: Multi-Health Systems; 2003.
Harms MB, Martin A, Wallace GL. Facial emotion recognition in autism spectrum disorders: a review of behavioral and neuroimaging studies. *Neuropsychol Rev*. 2010:20:290–322.
Hasson U, Avidan G, Gelbard H, Vallines I, Harel M, Minshew N, Behrmann M. Shared and idiosyncratic cortical activation patterns in autism revealed under continuous real-life viewing conditions. *Autism Res*. 2009:2:220–231.
Hatfield E, Cacioppo JT, Rapson RL. *Emotional contagion, emotional contagion*. Cambridge, England: Cambridge University Press; 1993
Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC. Grasping the intentions of others with one's own mirror neuron system. *PLoS Biol*. 2005:3:0529–0535.
Im DS. Template to perpetrate: an update on violence in autism spectrum disorder. *Harv Rev Psychiatry*. 2016:24:14–35.
Jabbi M, Swart M, Keysers C. Empathy for positive and negative emotions in the gustatory cortex. *NeuroImage*. 2007:34:1744–1753.
Jackson PL, Meltzoff AN, Decety J. How do we perceive the pain of others? A window into the neural processes involved in empathy. *NeuroImage*. 2005:24:771–779.
Jones AP, Happé FGE, Gilbert F, Burnett S, Viding E. Feeling, caring, knowing: different types of empathy deficit in boys with psychopathic tendencies and autism spectrum disorder. *J Child Psychol Psychiatry*. 2010:51:1188–1197.
Jüriloo A, Lauerma H, Holmalahti T, Tyni S, Aarnio J, Viitanen P, Wuolijoki T, Mattila A, Lintonen T, Joukamaa M, et al. Psychopathic traits in a representative sample of Finnish male prisoners. *Nord J Psychiatry*. 2014:68:117–122.
Kanne SM, Mazurek MO. Aggression in children and adolescents with ASD: prevalence and risk factors. *J Autism Dev Disord*. 2011:41:926–937.
Karjalainen T, Karlsson HK, Lahnakoski JM, Glerean E, Nuutila P, Jääskeläinen IP, Hari R, Sams M, Nummenmaa L. Dissociable roles of cerebral μ-opioid and type 2 dopamine receptors in vicarious pain: a combined PET-fMRI study. *Cereb Cortex*. 2017:27:4257–4266.
Keysers C, Gazzola V. Integrating simulation and theory of mind: from self to social cognition. *Trends Cogn Sci*. 2007:11:194–196.
Keysers C, Kaas JH, Gazzola V. Somatosensation in social perception. *Nat Rev Neurosci*. 2010:11:417–428.
Kiehl KA, Smith AM, Hare RD, Mendrek A, Forster BB, Brink J, Liddle PF. Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biol Psychiatry*. 2001:50:677–684.
Kim SY, Choi US, Park SY, Oh SH, Yoon HW, Koh YJ, Im WY, Park JI, Song DH, Cheon KA, et al. Abnormal activation of the social brain network in children with autism spectrum disorder: an fMRI study. *Psychiatry Investig*. 2015:12:37–45.
Leslie KR, Johnson-Frey SH, Grafton ST. Functional imaging of face and hand imitation: towards a motor theory of empathy. *NeuroImage*. 2004:21:601–607.
Levenson MR, Kiehl KA, Fitzpatrick CM. Assessing psychopathic attributes in a noninstitutionalized population. *J Pers Soc Psychol*. 1995:68:151–158.
Lockwood PL, Bird G, Bridge M, Viding E. Dissecting empathy: high levels of psychopathic and autistic traits are characterized by difficulties in different social information processing domains. *Front Hum Neurosci*. 2013:7:760.
Lord C, Rutter M, DiLavore P, Risi S, Gotham K, Bishop S. *Autism diagnostic observation schedule*. New York: Springer Reference; 2012.
Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, Jones EJH, Jones RM, Pickles A, State MW, et al. Autism spectrum disorder. *Nat Rev Dis Primers*. 2020:6(1):23.
Loureiro D, Machado A, Silva T, Veigas T, Ramalheira C, Cerejeira J. Higher autistic traits among criminals, but no link to psychopathy: findings from a high-security prison in Portugal. *J Autism Dev Disord*. 2018:48:3010–3020.
Lozier LM, Vanmeter JW, Marsh AA. Impairments in facial affect recognition associated with autism spectrum disorders: a meta-analysis. *Dev Psychopathol*. 2014:26:933–945.
Marsh AA. The neuroscience of empathy. *Curr Opin Behav Sci*. 2018:19:110–115.
Marsh AA, Cardinale EM. Psychopathy and fear: specific impairments in judging behaviors that frighten others. *Emotion*. 2012:12:892–898.
McIntosh DN, Reichmann-Decker A, Winkielman P, Wilbarger JL. When the social mirror breaks: deficits in automatic, but not voluntary, mimicry of emotional facial expressions in autism. *Dev Sci*. 2006:9:295–302.
Meffert H, Gazzola V, Den Boer JA, Bartels AAJ, Keysers C. Reduced spontaneous but relatively normal deliberate vicarious representations in psychopathy. *Brain*. 2013:136:2550–2562.
Müller JL, Gänßbauer S, Sommer M, Döhnel K, Weber T, Schmidt-Wilcke T, Hajak G. Gray matter changes in right superior tem-

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

poral gyrus in criminal psychopaths. Evidence from voxel-based morphometry. *Psychiatry Res Neuroimaging*. 2008:163:213–222.
Murrie DC, Cornell DG, Kaplan S, McConville D, Levy-Elkon A. Psychopathy scores and violence among juvenile offenders: a multimeasure study. *Behav Sci Law*. 2004:22:49–67.
Nummenmaa L, Glerean E, Viinikainen M, Jääskeläinen IP, Hari R, Sams M. Emotions promote social interaction by synchronizing brain activity across individuals. *Proc Natl Acad Sci U S A*. 2012:109:9599–9604.
Nummenmaa L, Lukkarinen L, Sun L, Putkinen V, Seppälä K, Karjalainen T, Karlsson H, Hudson M, Venetjoki N, Salomaa M, et al. Brain basis of psychopathy in criminal offenders and general population. *Cereb Cortex*. 2021:00:1–11.
O'Nions E, Tick B, Rijsdijk F, Happé F, Plomin R, Ronald A, Viding E. Examining the genetic and environmental associations between autistic social and communication deficits and psychopathic callous-unemotional traits. *PLoS One*. 2015:10.
O'Nions E, Lima CF, Scott SK, Roberts R, McCrory EJ, Viding E. Reduced laughter contagion in boys at risk for psychopathy. *Curr Biol*. 2017:27:3049–3055.e4.
Oberman LM, Winkielman P, Ramachandran VS. Slow echo: facial EMG evidence for the delay of spontaneous, but not voluntary, emotional mimicry in children with autism spectrum disorders. *Dev Sci*. 2009:12:510–520.
Ogai M, Matsumoto H, Suzuki K, Ozawa F, Fukuda R, Uchiyama I, Suckling J, Isoda H, Mori N, Takei N. fMRI study of recognition of facial expressions in high-functioning autistic patients. *Neuroreport*. 2003:14:559–563.
Parkes L, Fulcher B, Yücel M, Fornito A. An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. *NeuroImage*. 2018:171:415–436.
Pourtois G, Sander D, Andres M, Grandjean D, Reveret L, Olivier E, Vuilleumier P. Dissociable roles of the human somatosensory and superior temporal cortices for processing social face signals. *Eur J Neurosci*. 2004:20:3507–3515.
Pruim RHR, Mennes M, Buitelaar JK, Beckmann CF. Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. *NeuroImage*. 2015:112:278–287.
Raine A. Antisocial personality as a neurodevelopmental disorder. *Annu Rev Clin Psychol*. 2018:14:259–289.
Saarela MV, Hlushchuk Y, Williams ACDC, Schürmann M, Kalso E, Hari R. The compassionate brain: humans detect intensity of pain from another's face. *Cereb Cortex*. 2007:17:230–237.
Salmi J, Roine U, Glerean E, Lahnakoski J, Nieminen-Von Wendt T, Tani P, Leppämäki S, Nummenmaa L, Jääskeläinen IP, Carlson S, et al. The brains of high functioning autistic individuals do not synchronize with those of others. *NeuroImage Clin*. 2013:3:489–497.
van der Schalk J, Hawk ST, Fischer AH, Doosje B. Moving faces, looking places: validation of the Amsterdam Dynamic Facial Expression Set (ADFES). *Emotion*. 2011:11:907–920.
Scott SK, Lavan N, Chen S, McGettigan C. The social life of laughter. *Trends Cogn Sci*. 2014:18:618–620.
Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science (80-)*. 2004:303:1157–1162.
Spitzer RL, Williams JBW, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID): I: history, rationale, and description. *Arch Gen Psychiatry*. 1992:49:624–629.
Tiihonen J, Rossi R, Laakso MP, Hodgins S, Testa C, Perez J, Repo-Tiihonen E, Vaurio O, Soininen H, Aronen HJ, et al. Brain anatomy of persistent violent offenders: more rather than less. *Psychiatry Res Neuroimaging*. 2008:163:201–212.
Tiihonen J, Koskuvi M, Lähteenvuo M, Virtanen PLJ, Ojansuu I, Vaurio O, Gao Y, Hyötyläinen I, Puttonen KA, Repo-Tiihonen E, et al. Neurobiological roots of psychopathy. *Mol Psychiatry*. 2020:25:3432–3441.
Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*. 2002:15:273–289.
Uljarevic M, Hamilton A. Recognition of emotions in autism: a formal meta-analysis. *J Autism Dev Disord*. 2013:43:1517–1526.
Vecera SP, Marron MA. Book Review: Mindblindness: An essay on autism and theory of mind. *Q J Exp Psychol Sect A*. 1996:49:519–522.
Volynets S, Smirnov D, Saarimaki H, Nummenmaa L. Statistical pattern recognition reveals shared neural signatures for displaying and recognizing specific facial expressions. *Soc Cogn Affect Neurosci*. 2020:15:803–813.
Warren JE, Sauter DA, Eisner F, Wiland J, Dresner MA, Wise RJS, Rosen S, Scott SK. Positive emotions preferentially engage an auditory-motor "mirror" system. *J Neurosci*. 2006:26:13067–13075.
Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G. Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. *Neuron*. 2003:40:655–664.
Wild B, Erb M, Bartels M. Are emotions contagious? Evoked emotions while viewing emotionally expressive faces: quality, quantity, time course and gender differences. *Psychiatry Res*. 2001:102:109–124.
Wilson M. Without conscience: The disturbing world of the psychopaths among us. In: Hare RD, editors. *Criminal justice and behavior*. New York (NY): Guilford Press; 1994
Yang Y, Raine A, Narr KL, Colletti P, Toga AW. Localization of deformations within the amygdala in individuals with psychopathy. *Arch Gen Psychiatry*. 2009:66:986–994.

Downloaded from academic.oup.com/cercor/article/33/2/374/6553595 by OUP site access user on 19 October 2026

III

European Journal of Nuclear Medicine and Molecular Imaging (2026) 53:2069–2082
https://doi.org/10.1007/s00259-025-07620-5

ORIGINAL ARTICLE

Aberrant type 2 dopamine and mu-opioid receptor availability in autism spectrum disorder

Tuomo Noppari[1,2,3] · Jouni Tuisku[1,2] · Lasse Lukkarinen[1,2] · Pekka Tani[3] · Nina Lindberg[4] · Emma Saure[5] · Hannu Lauerma[6] · Jari Tiihonen[7,8,9] · Jussi Hirvonen[10] · Semi Helin[11] · Johan Rajander[12] · Juha Salmi[13] · Lauri Nummenmaa[1,2,14]

Received: 15 May 2025 / Accepted: 8 September 2025 / Published online: 18 October 2025
© The Author(s) 2025

Abstract

Purpose Opioid and dopamine receptor systems are implicated in the pathoetiology of autism, but in vivo human brain imaging evidence for their role remains elusive.

Methods Here, we investigated regional type 2 dopamine and mu-opioid receptor (D2R and MOR, respectively) availabilities and regional interactions between the two neuromodulatory systems associated with autism spectrum disorder (ASD). In vivo positron emission tomography (PET) with radioligands [11 C]raclopride (D2R) and [11 C]carfentanil (MOR) was carried out in 16 adult males with high functioning ASD and 24 age and sex matched controls. A whole brain voxel-wise analysis was tested with Student´s t-test and regional group differences in D2R and MOR receptor availabilities as total and separate were tested with linear mixed models also examining the associations between regional receptor availabilities with correlations.

Results There were no group differences in whole-brain voxel-wise analysis of D2R, but ROI analysis revealed a lower overall mean availability in striatum of the ASD compared to controls. Post hoc regional analysis revealed reduced D2R availability in nucleus accumbens and globus pallidus of the ASD group. The whole-brain voxel-wise analysis of MOR revealed cuneal/precuneal up-regulation in the ASD group, but there was no overall group difference in the ROI analysis for MOR. MOR down-regulation was observed in the hippocampi of the ASD group in a post hoc analysis. Regional correlations between D2R and MOR availabilities were weaker in the ASD group versus control group in the amygdala and nucleus accumbens.

Conclusions These alterations may translate to disrupted modulation of social motivation and reward in ASD.

Keywords Autism · Dopamine · Opioid · Positron emission tomography · MOR · D2R

✉ Tuomo Noppari
tuomo.noppari@hus.fi

[1] Turku PET Centre, University of Turku, Turku, Finland

[2] Turku University Hospital, Turku, Finland

[3] Department of Psychiatry, Helsinki University Hospital, Helsinki, Finland

[4] Department of Forensic Psychiatry, Helsinki University Hospital, Helsinki, Finland

[5] Clinicum, Department of Public Health, University of Helsinki, Helsinki, Finland

[6] Psychiatric Hospital for Prisoners, Health Care Services for Prisoners, Turku, Finland

[7] Department of Clinical Neuroscience, Karolinska Institute and Center for Psychiatry Research, Stockholm, Sweden

[8] Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland

[9] Neuroscience Center, University of Helsinki, Helsinki, Finland

[10] Department of Radiology, Turku University Hospital, Turku, Finland

[11] Radiopharmaceutical Chemistry Laboratory, Turku PET Centre, University of Turku, Turku, Finland

[12] Acceletor Laboratory, Turku PET Centre, Åbo Akademi University, Turku, Finland

[13] Unit of Psychology, Faculty of Education and Psychology, University of Oulu, Oulu, Finland

[14] Department of Psychology, University of Turku, Turku, Finland

Introduction

Autism spectrum disorder (ASD) is a developmental neuropsychiatric disorder with disabling difficulties in social communication and interaction and restricted and repetitive behavior [1]. ASD is strongly heritable with a complex genetic background [2, 3], but its neurochemical basis remains poorly understood. Aberrancies in different neuroreceptor systems [4] have been proposed to underlie ASD, but human studies have yielded only limited evidence for the role of specific neuroreceptor systems. Animal studies and neuropharmacological evidence, however, suggest that the endogenous dopamine and opioid systems might be the key molecular pathways underlying ASD [4–10].

Dopamine is released from the ventral tegmental area (VTA), which projects to the prefrontal cortex (PFC) and nucleus accumbens (NAcc) of the ventral striatum, forming the mesocorticolimbic circuit (MCL) that controls reward and motivated behavior [5, 11]. Dopamine released from substantia nigra pars compacta (SNpc), in turn, projects to the dorsal striatum (DS), forming the nigrostriatal (NS) pathway, controlling goal-directed and habitual behavior [5]. Dopamine receptors are divided into two main groups D1- (D1R, D5R) and D2-receptors (D2R, D3R, D4R), of which D1R and D2R moderate locomotion, reward, reinforcement, learning, and memory [12]. D1R are expressed as postsynaptic receptors widely across the brain and especially in the striatum [6, 13], while D2R is additionally expressed also as presynaptic auto-receptors, which modulate dopamine release in the synapses [14]. The use of dopaminergic agents, such as cocaine and methamphetamine, is associated with smaller social networks and impaired emotion recognition and emotional empathy [15]. Cocaine users also show difficulties in the theory of mind [16, 17] and display diminished emotional engagement and reward in social interaction [18, 19]. Functional magnetic resonance imaging (fMRI) studies in humans have suggested that the dysfunction of the MCL is associated with ASD [20–23]. Human positron emission tomography (PET) studies have further shown deviant dopamine signaling in ASD compared to controls, but the results have been controversial [24, 25]. There is also support for dopamine dysregulation in ASD from genetic studies [26]. Finally, dopamine antagonist medications such as risperidone and aripiprazole may alleviate autism symptoms, including irritability and stereotypic behavior [4–6, 27].

The endogenous opioid system controls a wide variety of human functions, from basic homeostasis and antinociception to emotions, social attachment, and reward [9, 28–31]. Neuropeptide beta-endorphin is released from hypothalamic nuclei and mesolimbic structures, projecting to other hypothalamic and corticolimbic structures, frontal lobes, brainstem, and periaqueductal grey [9, 28]. Beta-endorphin binds to three different opioid receptors, mu- (MOR), delta- (DOR), and kappa- (KOR), which are differentially distributed across the cortical and subcortical areas. Opioid receptors are widely expressed in the brain as postsynaptic receptors, but also as modulatory presynaptic auto-receptors [32]. Since the late seventies, opioid system dysfunctions have been proposed to be linked with autism [7, 9, 33, 34], and more recently, MOR knock-out mice were shown to manifest autism-related behaviors [10]. In animals, mu-opioid agonists also influence the social approach and withdrawal behavior depending on the dose, duration of dosing, and the social context [8]. Clinical studies in humans have shown that opiate addicts in maintenance treatment display deficits in social inference, emotion recognition and theory of mind [35–37]. Moreover, opioid antagonists may improve hyperactivity and restlessness symptoms in autism [4, 38]. The endogenous opioid system aberrancies in ASD have not been validated with any human imaging studies.

The interaction of the dopamine and opioid systems is critical for reward processing [39–42]. D2R and D1R are both expressed in the striatum and current theories suggest their opposing role in reward and aversion learning [14, 43]. Opioid mediated reward in turn depends on MOR activation in VTA, NAcc, amygdala, hippocampus, globus pallidus (GP) and medial frontal cortex (MFC) [44]. In animal microdialysis studies, mu-opioid agonists in the VTA increased the basal level of dopamine in the striatum, whereas antagonists decreased it [45, 46]. In human [11 C]carfentanil PET studies, the dopaminergic drug amphetamine has raised mu-opioid levels in the striatum, frontal cortex, thalamus, insula, and anterior cingulum (ACC) and cerebellum [47, 48]. Multiligand PET studies have confirmed that D2R and MOR availabilities correlate positively with each other in the striatum [49, 50],, and that this linkage may be disrupted in specific conditions such as morbid obesity [50]. Dysfunction of this opioid and dopamine modulated reward-system is associated with ASD and relates to aberrant social reward and motivation [8, 51, 52].

Here, we used in vivo PET with radioligands [11 C]raclopride (binding to D2R) and [11 C]carfentanil (binding to MORs) to compare regional receptor availabilities and the interactions between the receptor systems in ASD individuals and controls. We found that ASD is associated with striatal D2R basal availability downregulation and disruption of D2R and MOR interaction.

Materials and methods

Participants

Sixteen individuals with high-functioning ASD (mean age = 30 years, SD = 5, range = 23–42 years) and 24 controls (mean age = 29 years, SD = 9, range = 20–49 years) participated in the study. All participants gave informed, written consent and were compensated for their participation. The ethics board of the Hospital District of Southwest Finland approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. The study also obtained a research permit from the Hospital District of Helsinki and Uusimaa since the ASD group participants were largely recruited from this area. For minimizing confounding factors and maximizing statistical power, the study was run using a male-only sample with a restricted age range (20–50 years). General exclusion criteria for both groups were current use of narcotics, current abusive use of alcohol (over 14 units per week), severe axis I psychiatric illnesses, autoimmune illnesses, current medical conditions, and the standard MRI contraindications. Structural brain abnormalities that are clinically relevant or could bias the analyses were excluded by a consultant neuroradiologist.

Inclusion criterion for the ASD group was a valid autism spectrum disorder diagnosis (DSM-5 299.00). Participants in the ASD group were volunteers from the Helsinki and Turku University Hospital Neuropsychiatric Clinics, one participant was also recruited from Neuropsychiatric Clinic Proneuron, in Espoo. Diagnoses were verified by a neuropsychologist (JS), neurologist (TN), and psychiatrist (PT) following DSM-5 criteria based on patient history, all accessible information from birth records, well-baby clinics, and school healthcare. Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) assessment [53] was also performed by trained, research-reliable clinical psychologist (ES) to quantify the autism severity in this group. The ASD participants did not have any opioid or dopaminergic medication. Clinical information and characteristics of the ASD participants is found in Table S1.

Inclusion criteria for the control group were no history of neurological or psychiatric disorders. The control participants were screened for medical conditions from their patient histories and their use of prescribed medication was double-checked from the Finnish medical database. The control participants did not have any opioid or dopaminergic medication. Clinical information and characteristics of the control participants is found in Table S1.

All participants completed the Autism Spectrum Quotient (AQ) questionnaire for the evaluation of ASD-related traits (ASD group mean = 28, range = 23–42, SD = 6 and Controls group mean = 12, range = 4–27, SD = 5) [54, 55]. None of the participants had previous or current severe mental disorders based on the SCID-I interview [56]. The education of all the participants was classified into three different categories: (1) primary school, (2) secondary degree, (3) university degree. All the participants were also screened for their clinical status, with comprehensive general blood laboratory exams, including a urinary test for the use of narcotics.

The sample size was calculated based on comparable experiments on brain neurotransmission differences between groups [57]. In these experiments statistically significant differences in neuroreceptor binding could be established between two groups of 13 and 14 individuals with an effect size of d = 1.30. A priori power calculations with the G*Power software suggest that the predicted effects will be observed with a power of 0.90 with sample sizes exceeding 14.

Experimental design

PET imaging was carried out with General Electric (GE) Healthcare Discovery VCT (ASD n = 2, Controls n = 17) and Discovery 690 PET/CT (ASD n = 14, Controls n = 7) scanners in Turku PET center. Spatial resolution is similar (~ 5 mm FWHM) for both scanners [58, 59]. We measured MOR availability with high-affinity agonist radioligand [11 C]carfentanil [60] and D2R availability with agonist radioligand [11 C]raclopride, with the highest affinity to D2R, but also high affinity to D3R and low affinity to D4R [61, 62]. Radiotracer synthesis has been described previously [57, 63]. Both radioligands were administered as a rapid bolus injection, after which the radioactivity in the brain was measured for 51 min. Injected doses were 245 ± 11 MBq for [11 C]carfentanil and 254 ± 11 MBq for [11 C]raclopride). The [11 C]carfentanil and [11 C]raclopride PET imaging were performed on the same day >2.5 h apart. All PET images were reconstructed using 13 timeframes (3 × 1 min, 4 × 3 min, 6 × 6 min; total of 51 min). High-resolution anatomical T1-weighted images (TR 9.8 ms, TE 4.6 ms, flip angle 7º, 250 mm FOV, 256 × 256 voxel matrix with 1 mm^3 isotropic voxel size) were obtained with 3 T PET-MRI scanner (Philips Ingenuity TF PET-MR device, Philips Healthcare) for reference and normalization purposes. The PET-MR was not available for the lengthy dual-ligand scans for logistic reasons as it was used for clinical scans and other research projects necessitating MR at that moment.

PET preprocessing and modelling

PET images were preprocessed in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) using Magia pipeline [64] (https://github.com/tkkarjal/magia),

which utilizes SPM12 (The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, https://www.fil.ion.ucl.ac.uk/spm/software/spm12) in the PET data motion correction and image registration and FreeSurfer (version 6.3, https://freesurfer.net) in an automated region of interest (ROI) delineation. We used altogether twelve MOR binding ROIs involved in reward, motivation and socioemotional processing extracted from MRI by using FreeSurfer (striatal: caudate, globus pallidus (GP), NAcc, and putamen, extrastriatal: amygdala, thalamus, dorsal anterior cingulate cortices (dACC), rostral anterior cingulate cortices (rACC), OFC, posterior cingulate cortex (PCC), insula and hippocampus) [8, 23, 30–32, 44, 49, 51, 65–68]. Since raclopride binds reliably only in the striatum [69], we preferred the striatal ROIs from these to measure D2R binding [70–73], only with the exception of including thalamus and amygdala because of their striatal connections and relevance in ASD [23, 51, 52, 70, 74–79]. Reference tissues volumes (cerebellum for [11 C]raclopride and occipital cortex for [11 C]carfentanil) were automatically adjusted to account for specific radioligand binding, as described previously [64].

Specific regional binding of [11 C]raclopride and [11 C] carfentanil was quantified as binding potential relative to non-displaceable binding (BP_{ND}) using the simplified reference tissue model (SRTM) [80]. Parametric BP_{ND} images were also calculated for voxel-level analysis with basis function implementation of SRTM (bfSRTM) with 300 basis functions. Lower and upper bounds for theta parameter were set to 0.082 1/min and 0.6 1/min for [11 C]raclopride and 0.06 1/min and 0.6 1/min for [^{11} C]carfentanil. Before the parametric image calculation, the dynamic PET images were smoothed using a Gaussian kernel with 4 mm full width at half maximum to reduce the effect of noise in voxel-level bfSRTM fit. The resulting parametric images were further normalized into MNI152 space and smoothed again using a Gaussian 4 mm filter.

Statistical analysis

Full-volume analysis of the normalized and smoothed [11 C]raclopride and [11 C]carfentanil images was carried out with SPM12 using a two-sample Student's t-test, while controlling for scanner type. [11 C]carfentanil analysis included the whole brain volume, whereas voxel-wise [11 C]raclopride analysis was restricted to striatum, as BP_{ND} for this ligand can be reliably estimated only within this subregion [69]. The results were corrected for multiple comparisons by using false discovery rate (FDR) at $p < 0.05$.

Statistical analysis for the ROI data was performed using R software (version 3.5.1, The R foundation, Vienna, Austria) and linear mixed-effects models (LMMs), by including a random intercept to control for the potential differences between PET scanners. Before the LMM analysis, all BP_{ND} values were log-transformed to ensure normality. Normality of the model residuals was evaluated with the Shapiro-Wilk test and checked visually with density and Q-Q plots. Homogeneity of variance was verified separately for both scanners with Levene´s test. The results were corrected for multiple comparisons using Holm's method. The results are presented as percentage difference in BP_{ND} and regression effect estimates with 95% confidence intervals and p-values. We first tested for overall significant differences between the groups by including group as a fixed factor and participant, ROI and scanner type as random effects, allowing their intercepts to vary freely:

$$BPnd \sim 1 + group + (1|participant) + (1|scanner) + (1|roi)$$

As our primary interest with D2R availability was the striatum, the striatal ROIs were analyzed first separately and then together with the thalamus and amygdala ROIs [69].

We then set up post-hoc analysis for assessing group differences in each ROI separately, by specifying group as a fixed factor and scanner type as a random effect in LMM:

$$BPnd \sim group + (1|scanner)$$

The association between AQ scores and regional radioligand availability were analyzed with LMM, with AQ and age as a fixed factor and scanner type as a random effect:

$$BPnd \sim AQ + age + (1|scanner)$$

Associations between regional [11 C]carfentanil and [11 C] raclopride BP_{ND} were estimated using Pearson correlations. Group differences in the regional associations in D2R/MOR availability were tested using Fisher's z-test. A standard neuroimaging tool for matrix correlations, Mantel's test [81–83] was used to examine the similarity of the regional correlation structures of D2R/MOR availability between the groups.

Meta-analysis

To summarize the current data on striatal dopamine PET imaging studies in ASD we conducted a meta-analysis. A PubMed search was conducted on Oct. 3rd, 2023, using the keywords "autism spectrum disorder", "PET", "positron emission tomography" and "dopamine". Moreover, a complementary search with Google Scholar was conducted to confirm that no studies were missing. Finally,

we screened three of the latest review articles on the issue to ensure the full coverage of our research [24, 84, 85]. Altogether, we found nine potentially eligible articles [72, 74, 86–92], but only six included requisite data on striatal ROIs. Two of these six articles used the same data, so only one was included. Together with our results presented here a total number of six articles were included in the meta-analysis. All the articles were evaluated by three independent researchers of our group (TN, LN, JT) for inclusion in the meta-analysis. There was only one previous study using [11 C]raclopride tracer [72] measuring D2R availability, whereas the other studies used [18 F]FDOPA [87, 89–91] measuring presynaptic dopamine synthesis capacity or D1R binding [11 C]SCH23390 [88] as tracers (see Table S2 for more details). As one of the articles presented required data only in their supplemental figure and it was also not readily accessible from the authors, we used plot-digitizer tool to extract baseline values from the accessible figure [72]. Based on reported striatal group means, standard deviations and sample sizes we calculated the standardized mean difference (SMD, Cohen´s d) for each study and a pooled sample size weighted SMD with R software metafor package.

Results

Mean group-wise [^{11}C]raclopride and [^{11}C] carfentanil binding maps are shown in Fig. 1. Group-wise regional binding potentials for the radioligands are shown in Fig. 2.

D2R system

Whole-brain voxel-wise analysis did not reveal any significant group differences with [11 C]raclopride. The analysis with striatal ROIs revealed significant overall downregulation in D2R availability of the ASD group (Estimate 0.097, 95% CI [0.004,0.190], $p=0.048$). A complementary analysis, including extra-striatal regions thalamus and amygdala, revealed no group differences. Separate regional post-hoc analyses showed 13% lower BP_{ND} in the NAcc (Estimate 0.118, $100x(e^{0.118}-1)=13\%$, $p=0.034$, 95% CI [0.013,0.222], Shapiro $p=0.062$) and 19% lower BP_{ND} in globus pallidus (Estimate 0.175, $100x(e^{0.175}-1)=19\%$, $p=0.048$, 95% CI [0.008,0.343], Shapiro $p=0.230$) (Fig. 2, Table S3). BP_{ND} in the NAcc was also negatively correlated with AQ scores across all participants with one AQ point increase predicting a 0.5% decrease in NAcc BP_{ND} (Estimate −0.005, $p=0.058$, Shapiro $p=0.253$, $100x(e^{-0.005}-1)=0.5\%$), but this effect was not significant when the groups were analyzed separately (Fig. 3). The regional post-hoc analysis results did not survive correction for multiple comparison.

MOR system

Whole brain voxel-wise analysis revealed higher BP_{ND} in ASD participants compared to controls in the cuneal/precuneal cortex (BA 7,18,19&39, Cluster size 2069 K_E, cluster defining threshold $p<0.05$ (FDR-corrected), t=1.68, Cohen´s d=0.3) (Figure S1). ROI analysis revealed no

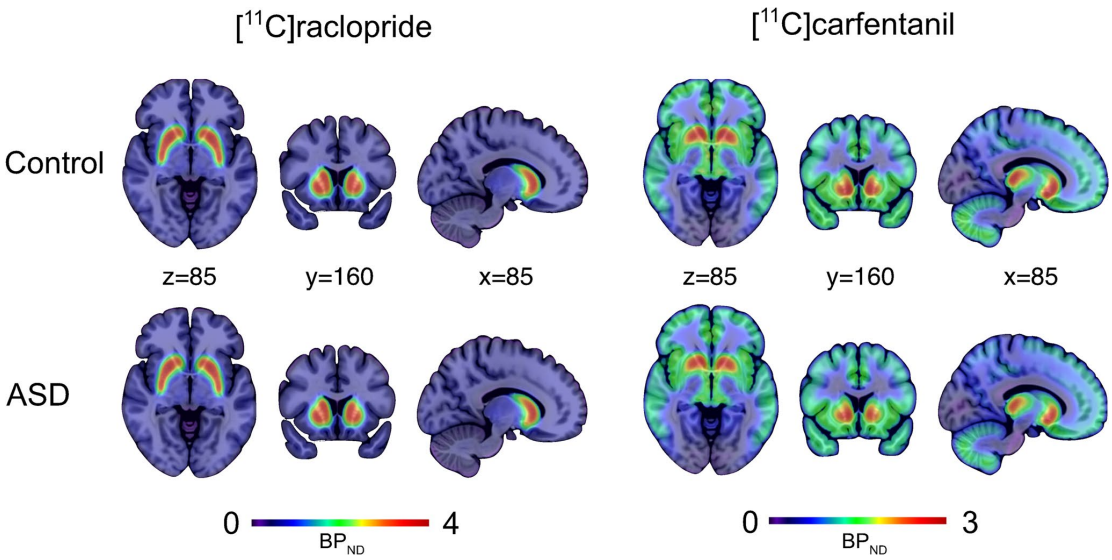


Fig. 1 Mean [11 C]raclopride and [11 C]carfentanil BP_{ND} in the control and ASD groups

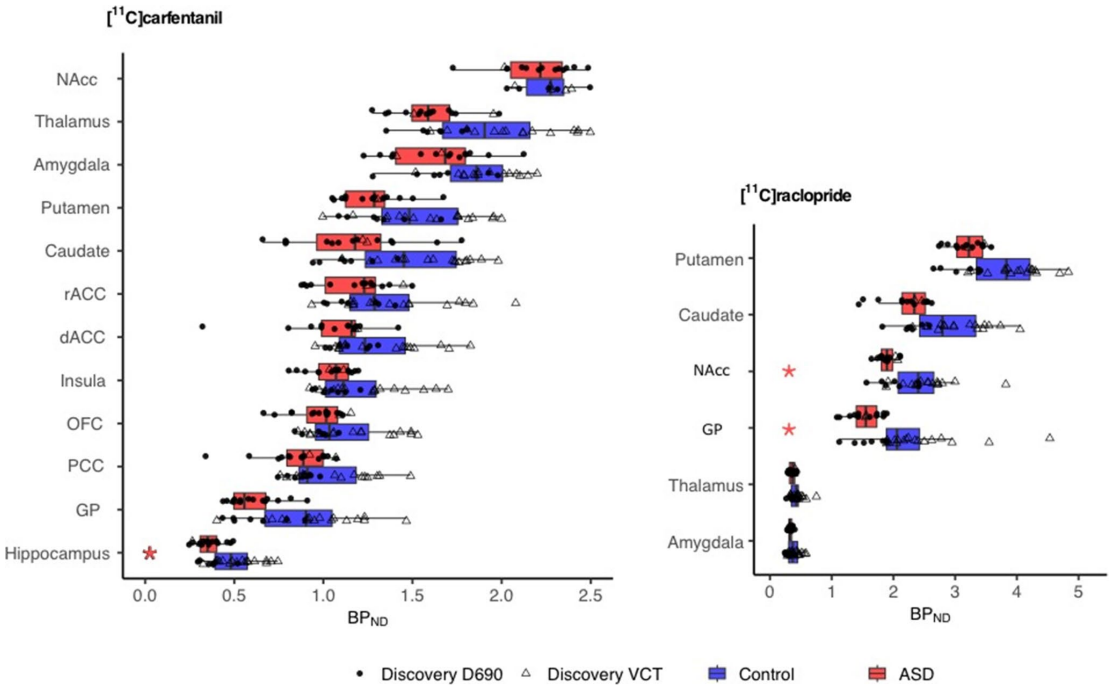


Fig. 2 Group-wise binding potentials of [11 C]raclopride and [11 C] carfentanil BP_{ND} in the predefined ROIs. The blue and red boxes mark the 2nd and 3rd quartiles, with the crossline marking the median of the data. Upper and lower whiskers mark 1.5 interquartile ranges from the box. Data with the two different scanners is marked with circles (Discovery 690) and triangles (Discovery VCT). Significant post-hoc differences between the groups are marked with an asterisk

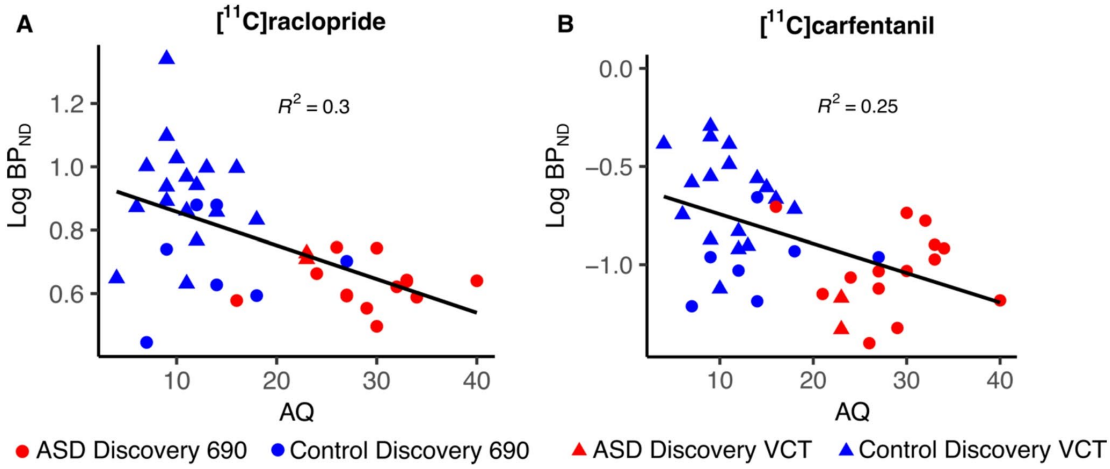


Fig. 3 Association and regression line between AQ scores and [11 C] raclopride BP_{ND} in the NAcc across the ASD and control groups (**A**). Association and regression line between AQ scores and [11 C]carfentanil BP_{ND} in the hippocampus (**B**). Data with the two different scanners is marked with circles (Discovery 690) and triangles (Discovery VCT)

overall differences between groups in MOR BP_{ND}. However, regional post-hoc analyses indicated 24% lower BP_{ND} for MOR in the hippocampus of ASD group (Estimate 0.214, $100x(e^{0.214} - 1) = 24\%$, $p = 0.022$, 95% CI [0.039,0.389], Shapiro $p = 0.381$) (Fig. 2, Table S3), but the results did not withstand multiple comparison. BP_{ND} in the hippocampus was also negatively correlated with AQ scores across all participants with one AQ point increase predicting a 1% decrease in NAcc BP_{ND} (Estimate −0.01, $p = 0.054$, Shapiro $p = 0.201$, $100x(e^{-0.01} - 1) = 1\%$), but this effect was not significant when the groups were analyzed separately (Fig. 3).

Dopamine-opioid interaction

In the control group, the BP_{ND} for [11 C]carfentanil and [11 C]raclopride correlated positively across all six ROIs that were analyzed with both ligands (Figs. 4 and 5). In the ASD group, significant correlation was only observed in thalamus (Figs. 4 and 5). The correlations were significantly stronger in the control versus ASD group in amygdala ($z = 2.48$ two-tailed $p = 0.013$) and NAcc ($z = 2.230$, two-tailed $p = 0.026$) (Figs. 4 and 5). The Mantel test did not indicate similarity between the D2R/MOR correlation matrices for control and ASD group ($r = 0.65$, $p = 0.16$).

Meta-analysis of PET-imaging data on dopamine systems in ASD

A fixed effect model showed a standardized mean difference (SMD) of −0.32 (−0.62, −0,03) with heterogeneity of 81.2% ($p < 0.001$), and a random model showed SMD of −0.25 (−1.06, 0.57) with heterogeneity of 85,6% ($p < 0.001$). We found a small overall effect of decreased dopamine tracer binding in ASD compared to controls (Fig. 6).

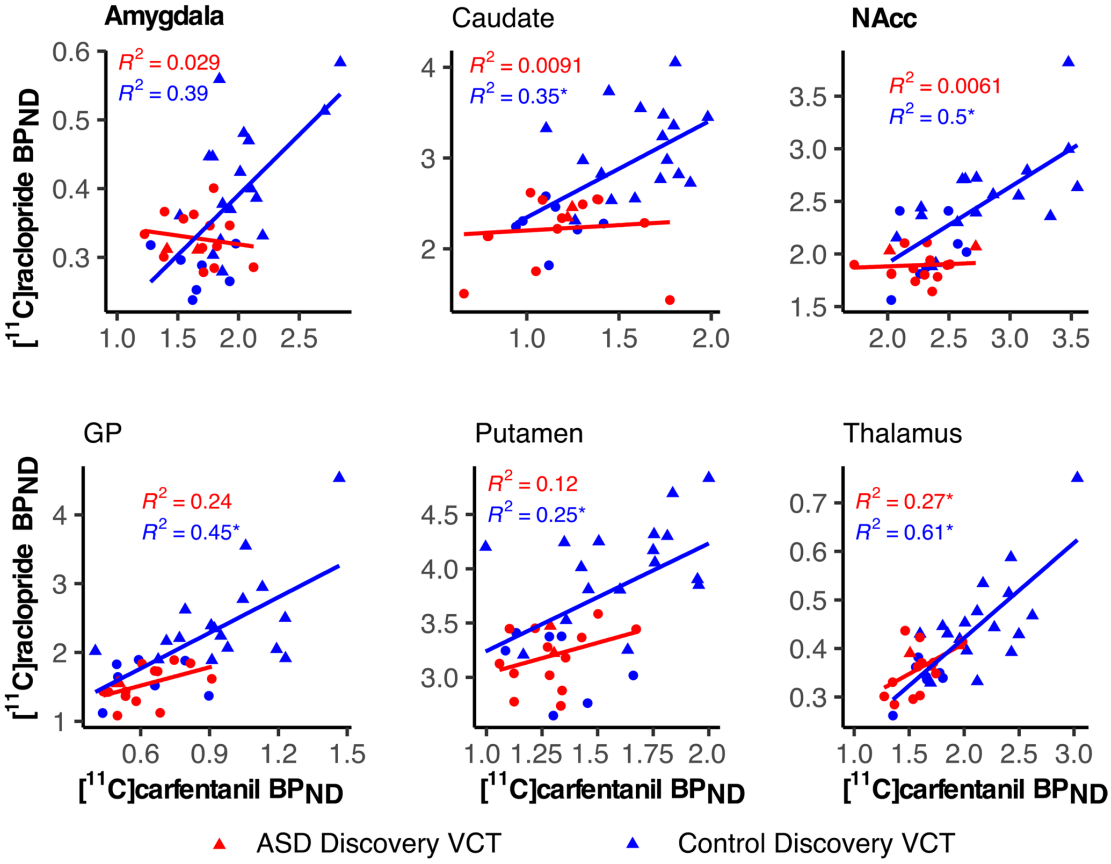


Fig. 4 Regional association and LS-regression lines between [11 C]carfentanil and [11 C]raclopride BP_{ND} in control and ASD groups. Significant within-group correlations are marked with an asterisk, and significant differences in correlations between groups (Amygdala and NAcc) with boldface

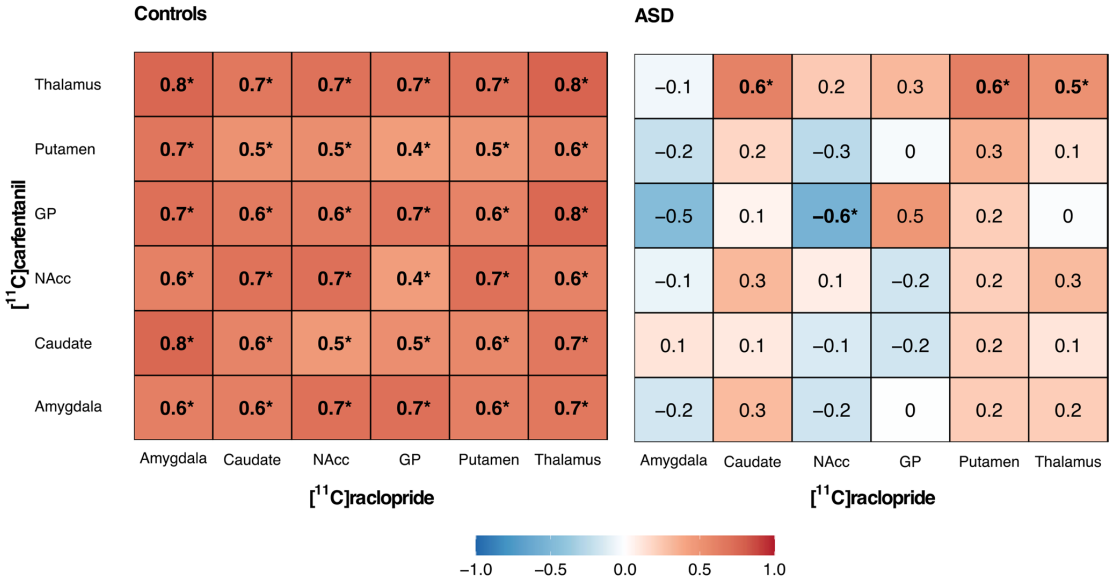


Fig. 5 Matrices showing interregional Pearson correlations between [11 C]carfentanil (rows) and [11 C]raclopride (columns) BP_{ND} in the control and ASD groups. Significant correlations are marked with boldface and asterisk

Discussion

Our main findings were that ASD is associated with downregulated striatal D2R availability and aberrant interaction between D2R and MOR systems. Alterations in the MOR system were restricted to the hippocampus and left cuneal/precuneal cortex. Altogether these data suggest that the dopaminergic system might be one of the neurotransmitter pathways linked with autism, also partly due to its aberrant interaction with the endogenous MOR system.

D2R system

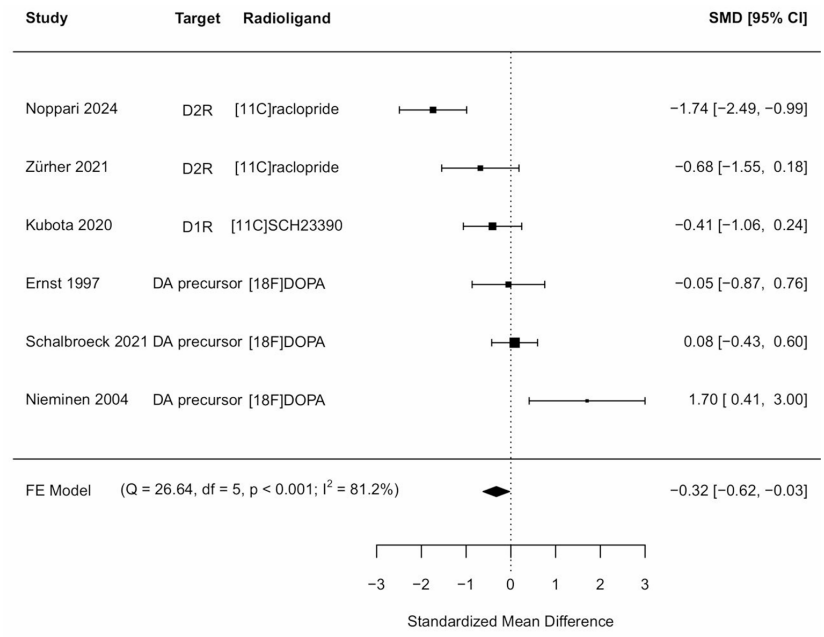
Mean BP_{ND} for [11 C]raclopride in the striatal ROIs was lower in the ASD compared to the control group. Our meta-analysis of the dopamine PET studies showed a small and heterogeneous overall effect of dopamine downregulation in ASD compared to controls. The studies using FDOPA reported either no differences or dopamine upregulation in the ASD compared to controls, while the other studies using [11 C]raclopride and [11 C]SCH23390 reported findings similar to ours. Differences in receptor availability, rather than dopamine synthesis capacity (measured by FDOPA), may thus be altered in ASD [93]. Striatal dopamine modulates social and nonsocial reward and motivation [5, 11], which may be disrupted in ASD, according to fMRI findings [21]. In animal studies, the striatal dopaminergic effects have been associated with stereotypic repetitive behavior [94], but the human imaging findings in ASD have not been conclusive [95].

The post-hoc ROI analysis revealed significantly lower BP_{ND} in the NAcc and GP in the ASD group than in the control group, and the AQ scores were also correlated with BP_{ND} in the NAcc across all participants. However, this finding has to be considered preliminary as it did not survive comparison for multiple comparison. In human fMRI studies, NAcc and GP have been associated with responses to reward and punishment [66, 96] and in animal studies, dopamine level in NAcc has been associated with prosocial behavior (increased release) or social avoidance in defeat situations (decreased release) [97].

These present D2R findings could relate, for instance, to aberrant social motivation and potentially explain atypical responses to social reward and high social avoidance in ASD [21, 23, 52, 97]. There are also possible links between striatal function and stereotypic repetitive behavior in ASD [94, 95]. However, none of these findings can be verified within the scope of this study, and further research is needed.

MOR system

The whole brain voxel-wise analysis showed a significant group difference in the left cuneal/precuneal cortex with higher BP_{ND} in the ASD group. The cuneus plays an essential role in primary visual processing [98]. Atypical connectivity of cuneal/precuneal and temporal areas



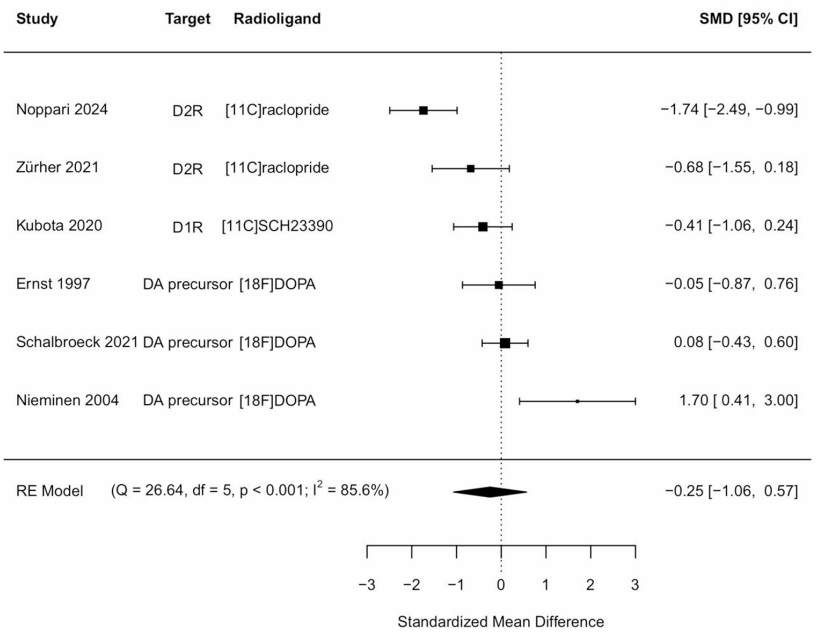


Fig. 6 Separate and pooled standardized mean differences (SMDs) in a meta-analysis of six striatal dopamine PET imaging studies with fixed (FE) and random effect (RE) models. Q = Cochran´s Q statistic, df = degrees of freedom, I^2 = inconsistency index

has been associated to ASD [99, 100]. Precuneus is one of the main areas of the Default Mode Network (DMN) critically involved in social cognition and showing dysfunction in ASD [101–105]. PET studies have shown significant distribution of opioid receptors in the human DMN, and opioids modulate its activity in a dose-dependent manner as the low opioid doses inhibit and the high doses enhance it [28]. Our previous study with a largely overlapping sample

revealed lower grey matter volume in the left precuneus of the ASD group [106]. The present study provides novel evidence that besides structural and functional alterations, also MOR functioning is abnormal in the precuneus area in individuals with ASD. This could play a role in explaining the symptom spectrum of ASD.

The post-hoc ROI analyses indicated lower BP_{ND} in the hippocampus in ASD participants compared to controls, and the AQ scores were also correlated with BP_{ND} in the hippocampus across all participants. However, the finding has to be considered preliminary as the group comparison did not withstand multiple comparison. There are fMRI studies demonstrating the involvement of the hippocampus in impaired perception of social emotions, as well as atypical learning, memory, and sensory hypersensitivity in ASD [107]. The hippocampus is also part of the MOR-modulated DMN and has stronger functional connectivity with other DMN regions in ASD compared to controls [107]. Moreover, the animal models of ASD present an impaired hippocampal neurogenesis, which has been found to be modulated by MOR. The more precise regulatory mechanisms are still unclear and the results are controversial [108–110]. Our findings on MOR availability could relate to impairments in social cognition and aberrant modulation of the DMN in ASD.

D2R and MOR system interaction

The BP_{ND} of [11 C]carfentanil and [11 C]raclopride showed high interligand correlations across the ROIs in the control group, while in the ASD group, significant interligand correlation was found only in the thalamus. Based on the direct comparison of the correlation strengths, the association between the two ligands was significantly stronger in the amygdala and NAcc of the control group compared to ASD group. In animal studies, both neurotransmitters have been associated with the modulation of motivational and rewarding aspects of social interaction [52, 111]. The NAcc has been identified as the key site for this dopamine and opioid modulation of social interaction, and the role of the amygdala has also been recognized in earlier studies [52, 76, 111, 112]. PET studies suggest a largely similar interaction between endogenous opioid and dopamine signaling in humans than observed in animals [47–49]. Interestingly, the interaction of these two neurotransmitters in NAcc is also implicated in the modulation of pain sensations [113, 114] that are both perceived and expressed abnormally in ASD [115]. While the existing knowledge of the aberrant pain modulation in ASD is still scarce [115], the previous and our present findings suggest a possible direction for further investigations.

Limitations

Despite our modest sample size, we found significant group differences and correlations to ASD symptoms in D2R and MOR systems. A more detailed examination of the role of these two neuromodulatory systems in different ASD symptom domains would require a larger sample size. Scanner hardware and software differences using two different PET scanners may contribute to data variability and could influence the results. However, due to the nested structure of our data, we attempted to statistically control for scanner differences by modelling a random intercept for each scanner. To reduce the heterogeneity in the ASD sample, we included only male participants, and therefore, our results may not be generalizable to the ASD population as a whole [116]. Further research is needed to examine if our findings can be replicated in females. Since ASD is not the only psychiatric disorder with features of social impairment [117], our findings might not be ASD specific and the role of dopaminergic dysfunction across other disorders warrants further studies [118]. Since [11 C]raclopride ligand bind to D2R/D3R and reflects receptor availability reliably only in the striatum, our findings should not be generalized to other mechanisms in the dopamine system (e.g., extra-striatal or D1R dopamine binding). Because D2R and D1R have an opposing role in reward and aversive learning, comparing both of these receptors could be beneficial in the future studies related to dopaminergic reward system and ASD [14, 43]. Since also [11 C]carfentanil binds specifically to MOR, our results should not be generalized to other mechanisms in the opioid system either (DOR, KOR). Moreover, our measurement was restricted to single baseline scans of [11 C]raclopride and [11 C]carfentanil binding, which reflect predominantly tonic receptor availabilities and do not reveal any precise neurotransmitter mechanisms behind them (e.g. postsynaptic/presynaptic, hypo/hyper dopaminergic or opioidergic function). A comparison between basal versus phasic task-related imaging protocols could help obtain more detailed functional interpretation for aberrant D2R and MOR systems in ASD. As our meta-analysis on striatal PET-studies included multiple different dopamine markers with varying functional roles, the results provide only a general overview on the striatal dopaminergic aberrancies in ASD, and additional data is needed for assessing the more specific effects of ASD on dopaminergic pathways.

Conclusions

Taken together, our findings reveal that ASD is associated with downregulated D2R availability and aberrant dopamine-opioid interaction in the striatum, as well as deviant

MOR availability in the areas related to DMN. These findings pave the way for new avenues to study the neuromolecular pathways leading to ASD symptoms and to develop related pharmacological treatments.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00259-025-07620-5.

Acknowledgements This study was supported by the Academy of Finland (grant numbers 294897 and 332225 to L.N); Finnish Governmental Research Funding (VTR) for Turku University Hospital (L.N.), Finnish Governmental Research Funding (VTR) for Helsinki and Turku University Hospital (T.N.).

Author contributions Conceptualization: [Pekka Tani, Nina Lindberg, Hannu Lauerma, Jari Tiihonen, Juha Salmitaival, Lauri Nummenmaa], Methodology: [Jouni Tuisku, Pekka Tani, Emma Saure, Hannu Lauerma, Jussi Hirvonen, Semi Helin, Johan Rajander, Juha Salmi, Lauri Nummenmaa], Formal analysis and investigation: [Tuomo Noppari, Jouni Tuisku, Lasse Lukkarinen], Writing - original draft preparation: [Tuomo Noppari, Jouni Tuisku]; Writing - review and editing: [Tuomo Noppari, Jouni Tuisku, Lasse Lukkarinen, Pekka Tani, Nina Lindberg, Emma Saure, Hannu Lauerma, Jari Tiihonen, Jussi Hirvonen, Semi Helin, Johan Rajander, Juha Salmi, Lauri Nummenmaa], Funding acquisition: [Tuomo Noppari, Nina Lindberg, Lauri Nummenmaa], Resources: [Nina Lindberg, Lauri Nummenmaa], Supervision: [Pekka Tani, Juha Salmi, Lauri Nummenmaa]. All authors read and approved the final manuscript.

Funding Open Access funding provided by University of Helsinki (including Helsinki University Central Hospital). This study was supported by the Academy of Finland (grant numbers 294897 and 332225 to L.N); Finnish Governmental Research Funding (VTR) for Turku University Hospital (L.N.), Finnish Governmental Research Funding (VTR) for Helsinki and Turku University Hospital (T.N.).

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics board of the Hospital District of Southwest Finland (15.12.2021/ETMK Dnro: 60/1801/2017 § 181, § 588) and the study also obtained a research permit from the Hospital District of Helsinki and Uusimaa (15.2.2021/HUS/161/2019 § 22, HUS/153/2021 § 1).

Consent to participate All participants gave informed, written consent and were compensated for their participation.

Competing interests The authors declare no competing financial interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Diagnostic and Statistical Manual of Mental Disorders [Internet]. DSM Library. [Cited 2023 Oct 17]. Available from: https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596
2. Tick B, Bolton P, Happé F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. J Child Psychol Psychiatry. 2016;57:585–95.
3. Woodbury-Smith M, Scherer SW. Progress in the genetics of autism spectrum disorder. Dev Med Child Neurol. 2018;60:445–51.
4. Marotta R, Risoleo MC, Messina G, Parisi L, Carotenuto M, Vetri L, et al. The neurochemistry of autism. Brain Sci. 2020;10:163.
5. Pavăl D, Miclutia I. The dopamine hypothesis of autism spectrum disorder revisited: current status and future prospects. Dev Neurosci. 2021;43:1–11.
6. Mandic-Maravic V, Grujicic R, Milutinovic L, Munjiza-Jovanovic A, Pejovic-Milovancevic M. Dopamine in Autism Spectrum Disorders—focus on D2/D3 partial agonists and their possible use in treatment. Front Psychiatry. 2022. https://doi.org/10.3389/fpsyt.2021.787097.
7. Panksepp J. A neurochemical theory of autism. Trends Neurosci. 1979;2:174–7.
8. Pellissier LP, Gandía J, Laboute T, Becker JAJ, Le Merrer J. μ opioid receptor, social behaviour and autism spectrum disorder: reward matters. Br J Pharmacol. 2018;175:2750–69.
9. Machin AJ, Dunbar RIM. The brain opioid theory of social attachment: a review of the evidence. Behaviour. 2011;148:985–1025.
10. Oddi D, Crusio WE, D'Amato FR, Pietropaolo S. Monogenic mouse models of social dysfunction: implications for autism. Behav Brain Res. 2013;251:75–84.
11. Reynolds LM, Flores C. Mesocorticolimbic dopamine pathways across adolescence: diversity in development. Front Neural Circuits. 2021. https://doi.org/10.3389/fncir.2021.735625.
12. Beaulieu J-M, Gainetdinov RR (2011). The Physiology, Signaling, and Pharmacology of Dopamine Receptors. Sibley DR, editor. Pharmacol Rev 63:182–217.
13. Jones-Tabah J, Mohammad H, Paulus EG, Clarke PBS, Hébert TE (2022) The Signaling and Pharmacology of the Dopamine D1 Receptor. Front Cell Neurosci [Internet]. [Cited 2024 Dec 9];15. Available from: https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2021.806618/full
14. Soares-Cunha C, Coimbra B, Sousa N, Rodrigues AJ. Reappraising striatal D1- and D2-neurons in reward and aversion. Neurosci Biobehav Rev. 2016;68:370–86.
15. Quednow BB. Social cognition and interaction in stimulant use disorders. Curr Opin Behav Sci. 2017;13:55–62.
16. Preller KH, Hulka LM, Vonmoos M, Jenni D, Baumgartner MR, Seifritz E, et al. Impaired emotional empathy and related social network deficits in cocaine users. Addict Biol. 2014;19:452–66.
17. Hulka LM, Eisenegger C, Preller KH, Vonmoos M, Jenni D, Bendrick K, et al. Altered social and non-social decision-making in recreational and dependent cocaine users. Psychol Med. 2014;44:1015–28.
18. Preller KH, Herdener M, Schilbach L, Stämpfli P, Hulka LM, Vonmoos M, et al. Functional changes of the reward system underlie blunted response to social gaze in cocaine users. Proc Natl Acad Sci U S A. 2014;111:2842–7.

19. Tobler PN, Preller KH, Campbell-Meiklejohn DK, Kirschner M, Kraehenmann R, Stämpfli P, et al. Shared neural basis of social and non-social reward deficits in chronic cocaine users. Soc Cogn Affect Neurosci. 2016;11:1017–25.
20. Dichter GS, Felder JN, Green SR, Rittenberg AM, Sasson NJ, Bodfish JW. Reward circuitry function in autism spectrum disorders. Soc Cogn Affect Neurosci. 2012;7(2):160–72.
21. Clements CC, Zoltowski AR, Yankowitz LD, Yerys BE, Schultz RT, Herrington JD. Evaluation of the social motivation hypothesis of autism: a systematic review and meta-analysis. JAMA Psychiatr. 2018;75:797.
22. Turner KC, Frost L, Linsenbardt D, McIlroy JR, Müller R-A. Atypically diffuse functional connectivity between caudate nuclei and cerebral cortex in autism. Behav Brain Funct. 2006;2:34.
23. Fuccillo MV (2016) Striatal Circuits as a Common Node for Autism Pathophysiology. Frontiers in Neuroscience. [cited 2024 Feb 2];10. Available from: https://www.frontiersin.org/articles/10.3389/fnins.2016.00027
24. Tan Z, Wei H, Song X, Mai W, Yan J, Ye W, et al. Positron emission tomography in the neuroimaging of autism spectrum disorder: a review. Front Neurosci. 2022;16:806876.
25. Zürcher NR, Bhanot A, McDougle CJ, Hooker JM. A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. Neurosci Biobehav Rev. 2015;52:56–73.
26. Kosillo P, Bateup HS. Dopaminergic dysregulation in syndromic autism spectrum disorders: insights from genetic mouse models. Front Neural Circuits. 2021. https://doi.org/10.3389/fncir.2021.700968.
27. Pavăl D. A dopamine hypothesis of autism spectrum disorder. Dev Neurosci. 2017;39:355–60.
28. Rocchi G, Sterlini B, Tardito S, Inglese M, Corradi A, Filaci G, et al. Opioidergic system and functional architecture of intrinsic brain activity: implications for psychiatric disorders. Neuroscientist. 2020;26:343–58.
29. Nummenmaa L, Tuominen L. Opioid system and human emotions. Br J Pharmacol. 2018;175:2737–49.
30. Nummenmaa L, Manninen S, Tuominen L, Hirvonen J, Kalliokoski KK, Nuutila P, et al. Adult attachment style is associated with cerebral μ-opioid receptor availability in humans: opioids and attachment. Hum Brain Mapp. 2015;36:3621–8.
31. Turtonen O, Saarinen A, Nummenmaa L, Tuominen L, Tikka M, Armio R-L, et al. Adult attachment system links with brain mu opioid receptor availability in vivo. Biol Psychiatry: Cogn Neurosci Neuroimaging. 2021;6:360–9.
32. Reeves KC, Shah N, Muñoz B, Atwood BK (2022) Opioid Receptor-Mediated Regulation of Neurotransmission in the Brain. Front Mol Neurosci [Internet]. [Cited 2024 Dec 7];15. Available from: https://www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2022.919773/full
33. Sahley TL, Panksepp J. Brain opioids and autism: an updated analysis of possible linkages. J Autism Dev Disord. 1987;17:201–16.
34. Kyte D, Jerram M, DiBiase R. Brain opioid theory of social attachment: a review of evidence for approach motivation to harm. Motiv Sci. 2020;6:12–20.
35. Gandolphe M-C, Lecluyse B, Triquet C, Brunelle E, Duparcq J-P, Nandrino J-L. Mind reading abilities in opiate-dependent patients: an exploratory study. Compr Psychiatry. 2018;83:46–52.
36. Eidenmueller K, Grimm F, Hermann D, Frischknecht U, Montag C, Dziobek I, et al (2021) Exploring Influences on Theory of Mind Impairment in Opioid Dependent Patients. Frontiers in Psychiatry [Internet]. [Cited 2023 Jun 29];12. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.721690
37. McDonald S, Darke S, Kaye S, Torok M. Deficits in social perception in opioid maintenance patients, abstinent opioid users and non-opioid users. Addiction. 2013;108:566–74.
38. Roy A, Roy M, Deb S, Unwin G, Roy A. Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions in children: a systematic review. J Intellect Disabil Res. 2015;59:293–306.
39. Margolis EB, Hjelmstad GO, Fujita W, Fields HL. Direct bidirectional μ-opioid control of midbrain dopamine neurons. J Neurosci. 2014;34:14707–16.
40. Wiskerke J, Schetters D, van Es IE, van Mourik Y, den Hollander BRO, Schoffelmeer ANM, et al. μ-opioid receptors in the nucleus accumbens shell region mediate the effects of amphetamine on inhibitory control but not impulsive choice. J Neurosci. 2011;31:262–72.
41. Escobar A del P, Casanova JP, Andrés ME, Fuentealba JA (2020) Crosstalk Between Kappa Opioid and Dopamine Systems in Compulsive Behaviors. Frontiers in Pharmacology [Internet]. [Cited 2023 Jun 27];11. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2020.00057
42. Rada P, Barson JR, Leibowitz SF, Hoebel BG. Opioids in the hypothalamus control dopamine and acetylcholine levels in the nucleus accumbens. Brain Res. 2010;1312:1–9.
43. Cox SML, Frank MJ, Larcher K, Fellows LK, Clark CA, Leyton M, et al. Striatal D1 and D2 signaling differentially predict learning from positive and negative outcomes. NeuroImage. 2015;109:95–101.
44. Fields HL, Margolis EB. Understanding opioid reward. Trends Neurosci. 2015;38:217–25.
45. Spanagel R, Herz A, Shippenberg TS. Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. Proc Natl Acad Sci USA. 1992;89:2046–50.
46. Devine DP, Leone P, Pocock D, Wise RA. Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: in vivo microdialysis studies. J Pharmacol Exp Ther. 1993;266:1236–46.
47. Mick I, Myers J, Stokes PRA, Erritzoe D, Colasanti A, Bowden-Jones H, et al. Amphetamine induced endogenous opioid release in the human brain detected with [11 C]carfentanil PET: replication in an independent cohort. Int J Neuropsychopharm. 2014;17:2069–74.
48. Colasanti A, Searle GE, Long CJ, Hill SP, Reiley RR, Quelch D, et al. Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. Biol Psychiatry. 2012;72:371–7.
49. Majuri J, Joutsa J, Arponen E, Forsback S, Kaasinen V. Dopamine synthesis capacity correlates with μ-opioid receptor availability in the human basal ganglia: a triple-tracer PET study. Neuroimage. 2018;183:1–6.
50. Tuominen L, Tuulari J, Karlsson H, Hirvonen J, Helin S, Salminen P, et al. Aberrant mesolimbic dopamine–opiate interaction in obesity. Neuroimage. 2015;122:80–6.
51. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The social motivation theory of autism. Trends Cogn Sci. 2012;16:231–9.
52. Kohls G, Chevallier C, Troiani V, Schultz R. Social wanting dysfunction in autism: neurobiological underpinnings and treatment implications. J Neurodev Disord. 2012;4:10.
53. Esler AN, Bal VH, Guthrie W, Wetherby A, Weismer SE, Lord C. The autism diagnostic observation schedule, toddler module: standardized severity scores. J Autism Dev Disord. 2015;45:2704–20.
54. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The Autism-Spectrum quotient (AQ): evidence from asperger Syndrome/High-Functioning Autism, Malesand Females, scientists and mathematicians. J Autism Dev Disord. 2001;31:5–17.
55. Bishop DVM, Maybery M, Maley A, Wong D, Hill W, Hallmayer J. Using self-report to identify the broad phenotype in parents of children with autistic spectrum disorders: a study

using the Autism-Spectrum quotient. J Child Psychol Psychiatry. 2004;45:1431–6.
56. Spitzer RL, Williams J, Gibbon M, First M. The structured clinical interview for DSM-III-R (SCID). I: history, rationale, and description. Arch Gen Psychiatry. 1992;49:624–9.
57. Karlsson HK, Tuominen L, Tuulari JJ, Hirvonen J, Parkkola R, Helin S, et al. Obesity is associated with decreased μ-Opioid but unaltered dopamine D_2 receptor availability in the brain. J Neurosci. 2015;35:3959–65.
58. Bettinardi V, Presotto L, Rapisarda E, Picchio M, Gianolli L, Gilardi MC. Physical performance of the new hybrid PET/CT discovery-690. Med Phys. 2011;38:5394–411.
59. Teräs M, Tolvanen T, Johansson JJ, Williams JJ, Knuuti J. Performance of the new generation of whole-body PET/CT scanners: discovery STE and discovery VCT. Eur J Nucl Med Mol Imaging. 2007;34:1683–92.
60. Eriksson O, Antoni G. [11 C]Carfentanil binds preferentially to μ-Opioid receptor subtype 1 compared to subtype 2. Mol Imaging. 2015;14:476–83.
61. Farde L, Hall H, Ehrin E, Sedvall G. Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. Science. 1986;231:258–61.
62. Seeman P, Tol HHMV. Dopamine receptor pharmacology. Trends Pharmacol Sci. 1994;15:264–70.
63. Nummenmaa L, Jern P, Malén T, Kantonen T, Pekkarinen L, Lukkarinen L, et al. μ-opioid receptor availability is associated with sex drive in human males. Cogn Affect Behav Neurosci. 2022;22:281–90.
64. Karjalainen T, Tuisku J, Santavirta S, Kantonen T, Bucci M, Tuominen L, et al. Magia: robust automated image processing and kinetic modeling toolbox for PET neuroinformatics. Front Neuroinform. 2020;14:3. https://doi.org/10.3389/fninf.2020.00003.
65. Weinstein AM. Reward, motivation and brain imaging in human healthy participants - a narrative review. Front Behav Neurosci. 2023;17:1123733.
66. Smith KS, Tindell AJ, Aldridge JW, Berridge KC. Ventral pallidum roles in reward and motivation. Behav Brain Res. 2009;196:155–67.
67. Hirvonen J, Aalto S, Hagelberg N, Maksimow A, Ingman K, Oikonen V, et al. Measurement of central μ-opioid receptor binding in vivo with PET and [11 C]carfentanil: a test-retest study in healthy subjects. Eur J Nucl Med Mol Imaging. 2009;36:275–86.
68. Manninen S, Tuominen L, Dunbar RI, Karjalainen T, Hirvonen J, Arponen E, et al. Social laughter triggers endogenous opioid release in humans. J Neurosci. 2017;37:6125–31.
69. Svensson JE, Schain M, Plavén-Sigray P, Cervenka S, Tiger M, Nord M, et al. Validity and reliability of extrastriatal [11 C]raclopride binding quantification in the living human brain. Neuroimage. 2019;202:116143.
70. Hirvonen J, Aalto S, Lumme V, Någren K, Kajander J, Vilkman H, et al. Measurement of striatal and thalamic dopamine D2 receptor binding with 11 C-raclopride. Nucl Med Commun. 2003;24:1207.
71. Seeman P, Wilson A, Gmeiner P, Kapur S. Dopamine D2 and D3 receptors in human putamen, caudate nucleus, and globus pallidus. Synapse. 2006;60:205–11.
72. Zürcher NR, Walsh EC, Phillips RD, Cernasov PM, Tseng C-EJ, Dharanikota A, et al. A simultaneous [11 C]raclopride positron emission tomography and functional magnetic resonance imaging investigation of striatal dopamine binding in autism. Transl Psychiatry. 2021;11:33.
73. Malén T, Karjalainen T, Isojärvi J, Vehtari A, Bürkner P-C, Putkinen V, et al. Atlas of type 2 dopamine receptors in the human brain: age and sex dependent variability in a large PET cohort. Neuroimage. 2022;255:119149.
74. Murayama C, Iwabuchi T, Kato Y, Yokokura M, Harada T, Goto T, et al. Extrastriatal dopamine D2/3 receptor binding, functional connectivity, and autism socio-communicational deficits: a PET and fMRI study. Mol Psychiatry. 2022;27:2106–13.
75. Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SCR. The amygdala theory of autism. Neurosci Biobehav Rev. 2000;24:355–64.
76. Atzil S, Touroutoglou A, Rudy T, Salcedo S, Feldman R, Hooker JM, et al. Dopamine in the medial amygdala network mediates human bonding. Proc Natl Acad Sci USA. 2017;114:2361–6.
77. Schuetze M, Park MTM, Cho IY, MacMaster FP, Chakravarty MM, Bray SL. Morphological alterations in the thalamus, striatum, and pallidum in autism spectrum disorder. Neuropsychopharmacol. 2016;41:2627–37.
78. Malén T, Santavirta S, De Maeyer S, Tuisku J, Kaasinen V, Kankare T, et al. Alterations in type 2 dopamine receptors across neuropsychiatric conditions: a large-scale PET cohort. NeuroImage: Clinical. 2024;41:103578.
79. Sato M, Nakai N, Fujima S, Choe KY, Takumi T. Social circuits and their dysfunction in autism spectrum disorder. Mol Psychiatry. 2023;28:3194–206.
80. Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. Neuroimage. 1996;4:153–8.
81. Baldassarre A, Filardi MS, Spadone S, Penna SD, Committeri G. Distinct connectivity profiles predict different in-time processes of motor skill learning. Neuroimage. 2021;238:118239.
82. Kheiri F, Bragin A, Engel J. Functional connectivity between brain areas estimated by analysis of gamma waves. J Neurosci Methods. 2013;214:184–91.
83. Reorganization of functionally connected brain subnetworks in high-functioning autism. [Cited 2025 Jun 30]; Available from: https://onlinelibrary.wiley.com/doi/10.1002/hbm.23084
84. Kowalewska B, Drozdz W, Kowalewski L. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) in autism research: literature review. Ir J Psychol Med. 2022;39:272–86.
85. Li X, Zhang K, He X, Zhou J, Jin C, Shen L, et al. Structural, functional, and molecular imaging of autism spectrum disorder. Neurosci Bull. 2021;37:1051–71.
86. Nakamura K, Sekine Y, Ouchi Y, Tsujii M, Yoshikawa E, Futatsubashi M, et al. Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. Arch Gen Psychiatry. 2010;67:59–68.
87. Nieminen-von Wendt TS, Metsähonkala L, Kulomäki TA, Aalto S, Autti TH, Vanhala R, et al. Increased presynaptic dopamine function in asperger syndrome. NeuroReport. 2004;15:757.
88. Kubota M, Fujino J, Tei S, Takahata K, Matsuoka K, Tagai K, et al. Binding of dopamine D1 receptor and noradrenaline transporter in individuals with autism spectrum disorder: a PET study. Cereb Cortex. 2020;30:6458–68.
89. Schalbroeck R, van Velden FHP, de Geus-Oei L-F, Yaqub M, van Amelsvoort T, Booij J, et al. Striatal dopamine synthesis capacity in autism spectrum disorder and its relation with social defeat: an [18F]-FDOPA PET/CT study. Transl Psychiatry. 2021;11:47.
90. Ernst M, Zametkin AJ, Matochik JA, Pascualvaca D, Cohen RM. Low medial prefrontal dopaminergic activity in autistic children. Lancet. 1997;350:638.
91. Schalbroeck R, de Geus-Oei L-F, Selten J-P, Yaqub M, Schrantee A, van Amelsvoort T, et al. Cerebral [18F]-FDOPA uptake in autism spectrum disorder and its association with autistic traits. Diagnostics. 2021;11:2404.
92. Fernell E, Watanabe Y, Adolfsson I, Tani Y, Bergström M, Hartvig P, et al. Possible effects of tetrahydrobiopterin treatment in six children with autism–clinical and positron emission tomography data: a pilot study. Dev Med Child Neurol. 1997;39:313–8.

93. Kanthan M, Cumming P, Hooker JM, Vasdev N. Classics in neuroimaging: imaging the dopaminergic pathway with PET. ACS Chem Neurosci. 2017;8:1817–9.
94. Langen M, Kas MJH, Staal WG, van Engeland H, Durston S. The neurobiology of repetitive behavior. mice… Neurosci Biobehavioral Reviews. 2011;35:345–55.
95. Langen M, Durston S, Kas MJH, Van Engeland H, Staal WG. The neurobiology of repetitive behavior: … and men. Neurosci Biobehav Rev. 2011;35:356–65.
96. Kohls G, Perino MT, Taylor JM, Madva EN, Cayless SJ, Troiani V, et al. The nucleus accumbens is involved in both the pursuit of social reward and the avoidance of social punishment. Neuropsychologia. 2013;51:2062–9.
97. Dai B, Sun F, Tong X, Ding Y, Kuang A, Osakada T, et al. Responses and functions of dopamine in nucleus accumbens core during social behaviors. Cell Rep. 2022;40:111246.
98. Cohen RA. Cuneus (2011) Encyclopedia of Clinical Neuropsychology [Internet]. Springer, New York, NY; [Cited 2025 Jun 19]. p. 756–7. Available from: https://link.springer.com/rwe/10.1007/978-0-387-79948-3_1356
99. Rolls ET, Zhou Y, Cheng W, Gilson M, Deco G, Feng J. Effective connectivity in autism. Autism Res. 2020;13:32–44.
100. Xiao Y, Wen TH, Kupis L, Eyler LT, Taluja V, Troxel J, et al. Atypical functional connectivity of Temporal cortex with precuneus and visual regions may be an early-age signature of ASD. Mol Autism. 2023;14:11.
101. Li W, Mai X, Liu C (2014) The default mode network and social understanding of others: what do brain connectivity studies tell us. Frontiers in Human Neuroscience [Internet]. [Cited 2023 Nov 10];8. Available from: https://www.frontiersin.org/articles/10.3389/fnhum.2014.00074
102. Harikumar A, Evans DW, Dougherty CC, Carpenter KLH, Michael AM. A review of the default mode network in autism spectrum disorders and attention deficit hyperactivity disorder. Brain Connect. 2021;11:253–63.
103. Borràs-Ferrís L, Pérez-Ramírez Ú, Moratal D. Link-level functional connectivity neuroalterations in autism spectrum disorder: a developmental resting-state fMRI study. Diagnostics. 2019;9:32.
104. Utevsky AV, Smith DV, Huettel SA. Precuneus is a functional core of the default-mode network. J Neurosci. 2014;34:932–40.
105. Wang Q, Li H-Y, Li Y-D, Lv Y-T, Ma H-B, Xiang A-F, et al. Resting-state abnormalities in functional connectivity of the default mode network in autism spectrum disorder: a meta-analysis. Brain Imaging Behav. 2021;15:2583–92.
106. Noppari T, Sun L, Lukkarinen L, Putkinen V, Tani P, Lindberg N, et al. Brain structural alterations in autism and criminal psychopathy. NeuroImage: Clinical. 2022;35:103116.
107. Banker SM, Gu X, Schiller D, Foss-Feig JH. Hippocampal contributions to social and cognitive deficits in autism spectrum disorder. Trends Neurosci. 2021;44:793–807.
108. Nam M-H, Won W, Han K-S, Lee CJ. Signaling mechanisms of μ-opioid receptor (MOR) in the hippocampus: disinhibition versus astrocytic glutamate regulation. Cell Mol Life Sci. 2021;78:415–26.
109. Zhang Y, Loh HH, Law P-Y. Effect of opioid on adult hippocampal neurogenesis. Sci World J. 2016;2016:1–7.
110. Liu C, Liu J, Gong H, Liu T, Li X, Fan X. Implication of hippocampal neurogenesis in autism spectrum disorder: pathogenesis and therapeutic implications. Curr Neuropharmacol. 2023;21:2266–82.
111. Vanderschuren LJMJ, Achterberg EJM, Trezza V. The neurobiology of social play and its rewarding value in rats. Neurosci Biobehav Rev. 2016;70:86–105.
112. Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW. Reward circuitry function in autism during face anticipation and outcomes. J Autism Dev Disord. 2012;42:147–60.
113. Harris HN, Peng YB. Evidence and explanation for the involvement of the nucleus accumbens in pain processing. Neural Regen Res. 2020;15:597.
114. Hagelberg N, Martikainen IK, Mansikka H, Hinkka S, Någren K, Hietala J, et al. Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity. Pain. 2002;99:273.
115. Bogdanova OV, Bogdanov VB, Pizano A, Bouvard M, Cazalets J-R, Mellen N, et al. The current view on the paradox of pain in autism spectrum disorders. Front Psychiatry. 2022. https://doi.org/10.3389/fpsyt.2022.910824.
116. Lai M-C, Lombardo MV, Auyeung B, Chakrabarti B, Baron-Cohen S. Sex/Gender differences and autism: setting the scene for future research. J Am Acad Child Adolesc Psychiatry. 2015;54:11–24.
117. Schilbach L. Towards a second-person neuropsychiatry. Philos Trans R Soc Lond B Biol Sci. 2016;371:20150081.
118. Lukkarinen L, Tuisku J, Sun L, Helin S, Karlsson HK, Venetjoki N, et al. Aberrant type 2 dopamine receptor availability in violent offenders with psychopathy. Neuroimage. 2024;297:120724.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

ISBN 978-952-84-3114-5 (Paperback)
ISBN 978-952-84-3113-8 (PDF)
ISSN 2954-2898 (Print)
ISSN 2954-2952 (Online)
Unigrafia, Helsinki
Printed in PunaMusta, Joensuu 2026